# The American Journal of Medicine



January 1952

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# The American Journal of Medicine

Vol. XII JANUARY, 1952 No. 1

## Editorial

Diagnosis of Diabetes Mellitus . . . . . . . . . . . . . . . . Russell M. Wilder 1

## Clinical Studies

## Relationship between Relapsing Pancreatitis and Essential Hyperlipemia Gerald Klatskin and Martin Gordon

This painstaking and extensive study of a case of relapsing pancreatitis with hyperlipemia and xanthomatosis, and review of the literature on the association of hyperlipemia with abdominal (particularly pancreatic) crises, makes several interesting points. It is likely that, as in the instance cited, the syndrome of relapsing pancreatitis with hyperlipemia is only a special case of the broad metabolic anomaly of essential familial lipemia, the pancreatitis being the result rather than the cause of lipemia. Excessive neutral fat in the blood might lead to fat embolism-like vascular occlusions. The authors discuss possible mechanisms and consequences of chylomicron clumping in this connection.

### Antithrombin Titer in Acute Pancreatitis

IRVING INNERFIELD, ALFRED ANGRIST AND JAMES W. BENJAMIN

The authors applied a method for determining the antithrombin titer to the problem of diagnosis in acute pancreatitis and found a significant rise to occur in fifty of fifty-five cases. The method would appear to be of value in differential diagnosis.

# Calcium, Potassium, Magnesium and Amylase Disturbances in Acute Pancreatitis Hugh A. Edmondson, Clarence J. Berne, Ralph E. Homann, Jr. and Maxine Wertman

The authors have drawn upon a large experience with acute pancreatitis to make some interesting observations, particularly in connection with the occurrence of hypocalcemia, hypokalemia and other electrolyte disturbances. The significance of these abnormalities is difficult to determine because of the frequency of complicating factors.

Contents continued on page 5

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gory is of necessity brief but the whole serves as an excellent orientating introduction to this field.

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This paper introduces a fine series of reviews of the most cogent aspects of our present knowledge of congenital heart disease. Dr. Bing has done a quite extraordinary job in compressing his classification of congenital heart disease into such a concise outline. Discussion of each cate-

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suggests that cortisone may be useful in such a situation, further trial being indicated.

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\*Spies, T. D.: Rehabilitation Through Better Nutrition, Philadelphia, W. B. Saunders Co., 1947, p. 62.

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1. Ebaugh, F. G.: Postgrad. Med. 4: 208, 1948.

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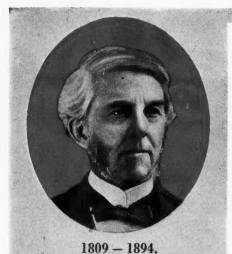
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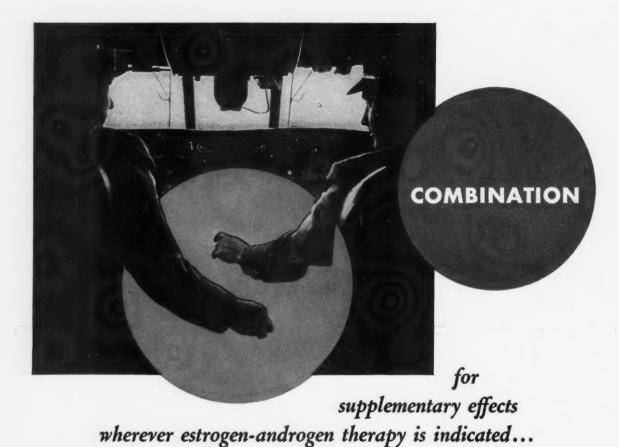
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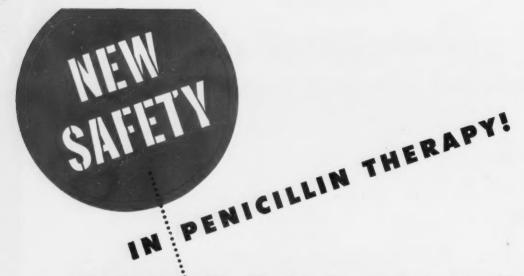
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## Editorial

## Diagnosis of Diabetes Mellitus

OYER and Womack<sup>1</sup> have again reviewed exhaustively the various methods of testing glucose tolerance, concluding that the one-dose standard glucose tolerance curve was the most valid as it was the most specific and most sensitive. Their criteria of normality with glucose ingestions limited to 1 or 1.5 gm. for each kg. of body weight were a fasting blood sugar of 120 mg. per cent or less and a two-hour level of 125 mg. per cent or less. The one-half and one-hour blood sugar levels, in their opinion, are without diagnostic significance inasmuch as high blood sugar levels at these times may mean little more than a rapid gastric emptying time. The value at three hours adds nothing that is not already demonstrated by the two-hour value. Many will agree with their conclusions that the diagnosis of diabetes mellitus can be based on these criteria, provided always that the patient has not been fasting or on a low carbohydrate diet prior to the test and that complications such as cirrhosis of the liver or one or another of several diseases of metabolism, notably hyperthyroidism and Cushing's disease, are not present as complications. There remain, however, with this test, as with others, cases in which diagnostic doubt remains, either because the one-hour level of blood sugar is quite abnormally high or because the return of this level to the fasting value has been delayed.

It therefore is of interest to find that data on the lactate and pyruvate levels of the blood, data obtained simultaneously with those of glucose in the glucose tolerance test, may in some cases add to the value of the test. Tolstoi2 noted a rise in blood lactate in diabetic patients when insulin was injected and Katayama and Killian<sup>3</sup> found that this rise was greater in normal subjects than in diabetics. Similar observations for pyruvate also have been reported. Himwich and Himwich4 observed that diabetic men and dogs formed pyruvate normally after muscular exertions but that they did not do so in response to ingested glucose. The subject was studied further by Horwitt, Hills and Kreisler<sup>5</sup> who noted that patients with moderately severe diabetes, when not receiving insulin, exhibited a rise in both blood lactate and blood pyruvate when glucose was ingested, but that these elevations were retarded. In the normal man the peak rise both of lactate and of pyruvate corresponded closely to that of the blood sugar whereas in the diabetic there was virtually no increase in the one-hour values of lactate and pyruvate. Also the high blood sugars and the delayed lactate and pyruvate response completely distorted the ratio between glucose and these two metabolites which, in normal subjects, at all points of the glucose tolerance curve remains roughly at the ratio of 100 to 10 to 1, in terms of milligrams per cent of glucose, lactic acid and pyruvic acid, respectively. When insulin was administered to these diabetic subjects, the lag in elevation of the lactate and pyruvate levels was in part corrected and the ratio mentioned was restored.

<sup>&</sup>lt;sup>3</sup> KATAYAMA, I. and KILLIAN, J. A. Changes in the sugar, inorganic phosphorus and lactic acid of animal and human blood after administration of insulin and of glucose. *J. Biol. Chem.*, 71: 707–722, 1927.

<sup>&</sup>lt;sup>4</sup> Німwісн, W. A. and Німwісн, H. E. Pyruvic acid in exercising depancreatized dogs and diabetic patients. *J. Biol. Chem.*, 165: 513–519, 1946.

<sup>&</sup>lt;sup>5</sup> HORWITT, M. K., HILLS, O. W. and KREISLER, O. Lactic and pyruvic acids in the blood after glucose and exercise in diabetes mellitus. *Am. J. Physiol.*, 156: 1, 1949.

<sup>&</sup>lt;sup>1</sup> MOYER, J. H. and WOMACK, C. R. Glucose tolerance: a comparison of four types of diagnostic tests in 103 control subjects and 26 patients with diabetes. *Am. J. M. Sc.*, 219: 161–173, 1950.

<sup>&</sup>lt;sup>2</sup> Tolstoi, E. The relationship of the blood glucose to the concentration of lactose in the milk of lactating diabetic women. *J. Clin. Investigation*, 14: 863, 1935.

In a recent thesis Hills<sup>6</sup> has extended these investigations to include thirty-four mild and "borderline" cases of diabetes mellitus and eleven subjects with the clinical diagnosis of Cushing's syndrome.

In most of the subjects with glucose tolerance curves which suggested diabetes mellitus but were not conclusively diagnostic the levels of lactate and pyruvate also proved to be equivocal. Although in some instances they provided evidence to support a more positive diagnosis, there seemed to be in general no sharp de-

<sup>6</sup> Hills, O. W. Blood lactic and pyruvic acid studies in diabetes mellitus and "Cushing's syndrome." Thesis, Graduate School of the University of Minnesota, Minneapolis, Minn., May, 1951.

marcation between normal and abnormal. In five of the eleven cases of Cushing's disease the glucose tolerance curves were normal. In these the levels of lactate and pyruvate also were essentially what would be expected in the normal. However, in six of the cases with Cushing's disease the glucose tolerance curves were frankly diabetic and in four of them the levels of lactate and pyruvate were increased to levels even higher than occurs in normal subjects and therefore very much above the levels attained in diabetes mellitus. In this respect, therefore, "steroid diabetes" was shown to differ strikingly from diabetes mellitus.

RUSSELL M. WILDER, M.D.

## Clinical Studies

# Relationship between Relapsing Pancreatitis and Essential Hyperlipemia\*

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HYPERLIPEMIA† is known to occur occasionally in association with attacks of pancreatitis. Speck¹ is credited with having described the first case in 1846, and since then ten‡ others have been reported.<sup>3–8</sup>

The pancreatitis in such cases is usually of the chronic relapsing variety<sup>4–8</sup> and the hyperlipemia, which is often not noted until several attacks have occurred, is due primarily to a marked increase in neutral fat<sup>3,4,7</sup> although there is often a concomitant but less marked rise in cholesterol<sup>3–7</sup> and phospholipid<sup>4–7</sup> concentration. The lipemia may clear with remarkable rapidity even before the abdominal symptoms have fully subsided,<sup>6</sup> but more often it persists during the symptom-free intervals between attacks.<sup>4,7,8</sup> It has been possible in some cases to lower the serum lipid level<sup>4,8</sup> and to reduce the frequency of the abdominal crises<sup>8</sup> by restricting the dietary intake of fat.

Occasionally the pancreatitis is accompanied

† The terms hyperlipemia and lipemia are used interchangeably here to signify a milky appearance of the serum or plasma due to a high concentration of lipids.

‡ The cases reported by Marchand<sup>9</sup> and Bernhard<sup>10</sup> have been omitted although they are included in the pancreatic lipemia group by some authors.<sup>2</sup> In the former, pancreatitis was a terminal complication of severe diabetic acidosis so that considerable doubt can be cast on the relationship of the pancreatitis to the lipemia. In Bernhard's case, on the other hand, there were no clinical or laboratory features to suggest pancreatitis, nor did the author himself believe it was present. Brunner<sup>3</sup> reported four cases but only one had frank lipemia. Marcus<sup>6</sup> reported four cases which will be indicated by the letters a,b,c,d following the reference number. Poulsen<sup>7</sup> reported two cases which will be lettered a and b. Speck's case<sup>1</sup> will be omitted from discussion because the original report was not available to us.

with xanthomatosis of the skin of the eruptive type<sup>4,60,8</sup> and by lipemia retinalis,<sup>4,7b</sup> conditions known to be manifestations of hyperlipemia.<sup>2,11,12</sup> The skin lesions may disappear when the dietary intake of fat is low and reappear when it is high.<sup>8</sup> Xanthomatosis has been observed before the onset of abdominal pain in some cases,<sup>4,8</sup> suggesting that hyperlipemia may precede the development of pancreatitis.

The early age at which the pancreatitis appears is a distinctive feature in this group. In the eight verified cases reported symptoms became manifest in early childhood in four<sup>4,6a,7a,7b</sup> and in early adult life in the remainder.<sup>3,6b,6c,8</sup> This is in striking contrast to the age incidence found in the more common type of relapsing pancreatitis, which generally affects the middleaged and seldom occurs in early life.<sup>13,14</sup> In a review of the literature up until 1948, Collett and Kennedy<sup>4</sup> could find only two reports of relapsing pancreatitis in children.

The pathogenesis of this syndrome is poorly understood. Most authors<sup>2-4,6,8</sup> have attributed the lipemia to an alteration in fat metabolism related to pancreatic insufficiency, an opinion based on the assumption that the pancreas exerts an hormonal control over lipid metabolism. However, there is little evidence to support this hypothesis. Chaikoff and his associates<sup>15-17</sup> have shown that the lipotropic activity of pancreatic extracts on the fatty liver of insulin-treated, depancreatized dogs is due not to an hormonal effect on fat metabolism, as suggested by Dragstedt et al., 18-20 but rather to the presence of an enzyme necessary for the absorption of bound methionine and choline in the diet. Moreover, it is difficult to attribute the

<sup>\*</sup> From the Department of Internal Medicine, Yale University School of Medicine, and the Department of Medicine, Veterans Administration Hospital, Newington, Conn. Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors. Aided by a grant from the Fluid Research Fund, Yale University School of Medicine.

lipemia of relapsing pancreatitis to pancreatic insufficiency on the basis of such animal experiments, since characteristically the serum lipid level falls following pancreatectomy in insulin-treated dogs.<sup>20,21</sup>

The only reports of serum lipid studies in animals with experimentally produced pancreatitis are contradictory. Binet and Brocq<sup>22</sup> observed transient increases in serum lipids in dogs with acute hemorrhagic pancreatitis, but Marcus<sup>4</sup> was unable to produce lipemia under similar conditions. Possibly the transient lipemia observed by Binet and Brocq was due to absorption of liquefied fat at sites of necrosis such as may occur in massive necrosis of the liver.<sup>23</sup>

Uncontrolled diabetes mellitus may give rise to hyperlipemia and xanthomatosis, but it does not appear to play any role in the pathogenesis of the syndrome under consideration. In only one of the reported cases was there any evidence of diabetes but it appeared after the xanthomatosis and was of insufficient severity to account for

hyperlipemia.

There are striking similarities between the syndrome of relapsing pancreatitis with hyperlipemia and that of idiopathic or essential familial lipemia, a constitutional disorder frequently accompanied with attacks of abdominal pain. Hitherto these have been regarded as unrelated entities.<sup>2</sup> However, recent observations have led us to the conclusion that the two diseases are identical and that pancreatitis, when it occurs in such cases, is the result rather than the cause of hyperlipemia. While this investigation was in progress, Poulsen<sup>7</sup> reported the occurrence of pancreatitis and hyperlipemia in two siblings and came to essentially the same conclusion.

The following is a report of studies carried out in a case of relapsing pancreatitis with lipemia and xanthomatosis. The results clearly indicated that the lipemia was familial in nature and suggested that the pancreatitis was the result of alterations in the physical state of the serum lipids leading to vascular occlusions.

#### CASE REPORT

R. J. K., (No. 56216) a twenty-two year old white male, was admitted to the hospital on June 19, 1950, complaining of severe non-radiating left upper quadrant pain of sixteen hours' duration. The onset was sudden and there were no associated symptoms until one hour

before entry to the hospital when vomiting occurred.

In 1946, while still in military service, the patient had suffered a similar attack of abdominal pain necessitating surgical exploration. This revealed an acute necrotizing pancreatitis, extensive mesenteric fat necrosis and multiple adhesions in the region of the duodenum. Three weeks later a small segment of jejunum had been resected because of a complicating jejunal fistula. Following slow convalescence the patient was discharged from the hospital free of symptoms. Until the onset of the present illness, four years later, he had remained well.

Approximately three months before the first attack of abdominal pain in 1946 the patient had noted the appearance of a yellow, papular rash on the extremities. The lesions increased in number until the occurrence of the pancreatitis and then slowly faded over a period of several months. In March, 1950, three months prior to the onset of the present attack, similar lesions began to appear over the knees. These spread slowly to involve the thighs, legs and feet. Somewhat similar lesions appeared on the hands but these differed from the others in that they seemed to be beneath the skin and were often painful after slight trauma.

The patient had never been obese and had never eaten to excess, but on the occasion of both attacks of abdominal pain he was found to be 15 pounds over his usual weight of 120 pounds.

Venous blood had been drawn on numerous occasions in the past, and especially during his previous hospitalization for pancreatitis, but at no time had any attending physician commented on its appearance to the patient.

Except for an operation on the left kidney for an alleged streptococcal infection in 1935, at the age of seven, the patient had enjoyed excellent health and denied having had any illnesses of consequence. His diet had always been well balanced and at no time had he noted intolerance for specific foods or any other gastrointestinal symptoms. A system review likewise failed to disclose any complaints. The intake of alcoholic beverages had always been negligible.

The patient was the only child of divorced parents, both of whom were living and well. There was no history of diabetes, xanthomatosis, recurrent abdominal pain or vascular disease on either side of the family. Subsequently, the mother and father were interviewed to confirm these facts and on examination neither showed

any evidence of xanthomatosis. The patient was married but had no children.

On admission to the hospital the patient was obviously in acute distress, groaning with agonizing abdominal pain, but he did not appear to be in a state of shock and his vital signs were only slightly altered. The temperature was 99.4°F., the pulse 80 and the blood pressure 120/90. He was well developed and well nourished and showed a mild degree of dehydration. The most striking findings were confined to the skin and abdomen. Over the medial and anterior aspects of the thighs and about the wrists there were numerous round, firm, sharply circumscribed, yellowish papules which had the characteristic appearance of xanthomas. A single papule was also noted on the neck just beneath the chin. The lesions were dome-shaped and fairly uniform in size, measuring approximately 5 mm. in diameter, and appeared to be located in the superficial layers of otherwise normal skin. No lesions were evident in the mucous membranes and there were no xanthomas of the eyelids, arcus juvenilis, tendon nodules or lipemia retinalis.

The abdomen was flat and exhibited a broad midline scar with a small central incisional hernia. There were signs of generalized peritoneal irritation, most marked in the left upper quadrant, with spasticity of the abdominal wall and exquisite tenderness, especially on rebound. There was no evidence of free fluid and peristalsis was not audible. The liver, spleen and kidneys could not be felt and there were no other palpable abdominal masses. No tenderness or masses were made out on rectal examination. Except for a soft, grade I systolic murmur at the apex of the heart, no other abnormalities were noted in the remainder of the examination.

In view of a presumptive diagnosis of recurrent acute pancreatitis, conservative supportive therapy in the form of parenteral fluids and opiates was instituted. During the night the patient's condition remained good but the following morning he lapsed into a state of shock and exhibited increased signs of peritoneal irritation. A serum amylase level of 1,225 units (normal less than 200) at this time confirmed the clinical diagnosis of pancreatitis. The shock responded to multiple transfusions of whole blood and plasma, and abdominal distention and vomiting were readily controlled by constant gastric suction. However, the patient's condition remained critical for several days, and

remittent fever and signs of peritonitis did not subside until the tenth day. During this period abdominal pain was severe and constant, requiring large and frequent doses of opiates for relief. Even after subsidence of the peritonitis, however, the patient continued to experience frequent attacks of abdominal pain intermittently.

The serum drawn the day of admission was found to be grossly lipemic, but by the end of a week it had cleared. Unfortunately no further data are available on the appearance of the serum during this admission.

Because of the persistence of pain for more than two weeks and the history of a previous attack, a bilateral splanchnic nerve resection was recommended by the attending surgeon. This procedure was carried out in two stages on July 5th and 21st, the splanchnic nerves and the dorsal sympathetic chains from  $D_5$  to  $D_{12}$  being excised transthoracically. The postoperative course was uneventful except for severe chest pain. Following the second stage there was transient hypotension but this was readily controlled by the use of an abdominal binder and elastic leg bandages.

During the two weeks following his second operation the patient had no abdominal pain and began to regain some of the 30 pounds he had lost during the preceding month. The xanthomas, which were stationary for the first few weeks of his illness, began to get smaller and disappeared completely by the end of the first month.

Since the patient's general condition seemed good, he was granted a two weeks' leave of absence from the hospital on August 5th. Ten days later, however, he was obliged to return because of a recurrence of the pain which had gotten progressively worse over a three-day period. Although he was afebrile and showed less striking abdominal signs than previously, he was in a state of mild shock and had an elevated serum amylase level of 555 units. During the following week there was considerable pain and a progressive rise in the serum amylase level, reaching a peak of 2,160 units on August 22nd. Nevertheless, it was the opinion of the surgeons who had previously attended him that this attack was considerably milder than the others. However, he continued to have frequent, mild, recurrent abdominal pain for another two weeks, and it was not until September 4th that the serum amylase level reached normal. By September 9th he was sufficiently recovered to

permit his discharge from the hospital. When he was seen again in the outpatient department on October 8th, he reported that he had had attacks of abdominal pain at weekly intervals since discharge from the hospital. These were of several hours' duration, unrelated to the ingestion of food, and frequently required opiates for relief.

Twelve days later on October 20th it was necessary to admit the patient to the hospital for the third time because of increasing epigastric and mid-abdominal pain. For several days it had been present almost constantly and had been accompanied with persistent vomiting. The patient was somewhat drowsy and dehydrated but his temperature and pulse were normal. The blood pressure was down to 96/60 and there was marked tenderness and spasm of the abdomen, especially in the epigastrium. Although the diagnosis of recurrent pancreatitis seemed probable, the serum amylase level was found to be normal (125 units). At this time the possibility was considered that many of his symptoms were psychogenic in origin and that the patient was becoming addicted to drugs. Accordingly, narcotics were withheld and a psychiatric consultation was obtained. The psychiatrist found evidence of marked emotional tension and recommended more thorough psychiatric investigation and therapy. However, since the pain had subsided without treatment, the patient was unwilling to stay for such treatment and left the hospital on October 30th. It is noteworthy that the serum was lipemic once again during this admission. Also, several new xanthomatous lesions were noted on the thighs and wrists.

Three weeks later on November 20th the patient was admitted to the hospital for the fourth time in five months. He had been suffering from severe abdominal pain and vomiting for several days which had not been relieved by opiates. He was pale, cold and clammy and appeared to be in shock. His temperature was 101°F., pulse 104 and blood pressure 100/80. There was marked generalized abdominal tenderness and spasm without distention or signs of free fluid. The liver, spleen and kidneys were not palpable. No skin xanthomas were observed and there was no evidence of lipemia retinalis. The serum amylase and lipase levels were both abnormally high (585 units and 7.4 ml., respectively). Shortly after admission the blood pressure fell to 80/60. Following the intravenous

administration of whole blood and fluids the patient's condition improved but severe pain and abdominal distention necessitating continuous gastric suction persisted for four days. Thereafter for a period of six days there was mild pain and vomiting intermittently and a remittent low grade fever.

The appearance of the serum on admission was not stated but four days later it was found to be clear.

On the tenth day, November 29th, two hours following the completion of an infusion of 500 ml. of saline and 500 ml. of 10 per cent glucose, the patient suddenly experienced marked weakness and a cold sweat, unaccompanied with pain, and was found to be in a mild state of shock with a blood pressure of 90/60 and a pulse rate of 70. Abdominal examination at this time revealed no abnormalities. Following another infusion of glucose and saline there was a transient rise in blood pressure but an hour later it fell to 86/44 and was associated with an even more marked bradycardia. The attack lasted six hours and appeared to subside following a transfusion of whole blood. The serum amylase was normal but the serum lipase was slightly increased (1.9 ml.) and remained so for several days.

During the following week the patient felt well and required only occasional medication for pain. However, severe abdominal pain and shock recurred on December 11th and 12th but were of only brief duration.

At this time the patient was seen by one of us who suggested the possibility that the pancreatitis might be secondary to essential hyperlipemia and therefore amenable to dietary treatment. Accordingly, a low fat diet containing 20 gm. of fat, 90 gm. of protein and 285 gm. of carbohydrate was started on December 16th. Almost at once there was a dramatic improvement in the patient's condition. He volunteered the information that it was the first time in six months that he had felt completely well. He was observed for a period of three months and on March 20, 1951,\* reported that not once during that period had he experienced pain or required medication. His serum became less lipemic but never became entirely clear. The few remaining

<sup>\*</sup>The patient was seen again in August, 1951, at which time his serum was clear. There were no skin xanthomas and he reported that he had had no abdominal pain since December, 1950.

xanthomatous skin lesions which had appeared in November cleared.

A number of special studies were carried out during this period which will be described subsequently.

The laboratory data were as follows: The erythrocyte count and hemoglobin concentration which were determined at frequent intervals were always found to be within normal limits. The leukocyte count and differential smear were likewise normal, except following both stages of the splanchnic nerve resection when there was mild leukocytosis, 12,350 and 17,050. On two occasions during the third admission there was mild leukopenia, 4,100 and 4,750, associated with attacks of abdominal pain.

Frequent urinalyses were carried out and, except for transient glycosuria associated with infusions of glucose and a trace of albumin on several occasions, no abnormalities were found. The blood sugar level was determined on nine occasions. It was usually normal, ranging from 75 to 100 mg. per cent, but on two occasions during the first admission values of 170 and 123 mg. per cent were found. These coincided with periods when the patient was receiving glucose infusions. Serum calcium concentration was determined on four occasions and was found to be slightly below normal during the acute phase of two attacks of pancreatitis; June 21, 1950, 9.2 mg.; June 23rd, 8.4 mg.; November 21st, 8.4 mg.; November 24th, 9.6 mg. per cent. Serum inorganic phosphorus on June 23rd was 2.4 mg. per cent. Serum non-protein nitrogen was determined on seven occasions and was always below 40 mg. per cent except on June 21st and July 22nd, when it was slightly above normal in association with some degree of dehydration (43 and 58 mg. per cent). Serum bicarbonate and chloride concentrations were determined on several occasions and were always within normal limits. Gastric analysis on October 23rd revealed fasting volume 15 ml., free HCl 0 ml.: after subcutaneous histamine, volume 0.5 ml., total acid 34 ml., free HCl 12 ml. On February 6, 1951, the fasting specimen was: total acid 26 ml., free HCl 0 ml. Liver function tests showed the icterus index was increased during the first attack of pancreatitis, June 21, 1950, 22 units; June 29th, 23 units; July 4th, 24 units; July 6th, 14 units and July 21st, 17 units. Serum alkaline phosphatase on June 21st was 2.7 Bodansky units. Complete studies on October 25th revealed bromsulphalein retention (45 minutes following an injection of 5 mg. of dye per kg.) 0 per cent, cephalin-cholesterol flocculation negative, thymol turbidity 22.4 units, serum alkaline phosphatase 4.6 Bodansky units; prothrombin 90 per cent of normal. Studies repeated on January 8, 1951, revealed bromsulphalein retention 1.5 per cent, cephalin-cholesterol flocculation 2+, thymol turbidity 9.8 units, alkaline phosphatase 4.9 Bodansky units. Mazzini test for syphilis was negative on June 19, 1950, October 23, 1950 and January 21, 1951. Electrocardiogram was within normal limits.

X-ray studies of the abdomen on June 21st, August 22nd and October 20, 1950, were normal; no evidence of pancreatic calcification was seen. Chest x-ray on July 14th showed pleural thickening at right base (nine days following right splanchnic nerve resection); on July 26th there was left pleural effusion (five days following left splanchnic nerve resection); October 20th, normal except for pleural thickening of left costophrenic angle. On August 25th the cholecystogram was normal. The gastrointestinal series on August 28th was normal.

Frozen section of one of the previously described skin papules revealed a large collection of foam cells compatible with the diagnosis of xanthomatosis. Unfortunately the specimen was not saved for permanent mounting so it could not be re-examined for a detailed description of its structure. A biopsy specimen obtained with a Vim-Silverman needle on December 22, 1950, revealed normal liver tissue without evidence of foam cells or fatty infiltration; the Kupffer cells contained a moderate amount of pigment which had the staining properties of iron. This hemosiderosis was thought to be related to the previously administered transfusions of whole blood. Bone marrow biopsy revealed normal marrow tissue without evidence of foam cells (December 19, 1951).

#### SERUM LIPID STUDIES

Fractions. It is evident from the data in Table 1 that the lipemia was due to a striking increase in neutral fat. Its concentration ranged between 13.0 and 46.0 mEq./L. under varying conditions, values considerably in excess of the normal of  $3.12 \pm 1.49$  mEq. previously reported from this laboratory.<sup>24</sup>

The serum cholesterol concentration usually fell within the normal range of  $194 \pm 36$  mg. per cent,<sup>24</sup> even when marked lipemia was

JANUARY, 1952

SERUM LIPID STUDIES

Pate	Total Fatty Acids (mEq./L.)		Cholesterol Total Free (mg.%) (mg.%)	Free Total	Lipid P (mg.%)	Cholesterol Esters (mEq. A.)	Fatty Acids Phospho- lipids (mEq./L.)	Fat (mEq. A.)	Neutral Fat (mg.%)	Phospho- lipids (mg.%)	Total Lipids (mg.%)	Abdominal Paint	Serum Amylase § (units)	Remarks
6/20/50 6/21/50 6/21/50		1										###	395	After regular diet (1946–1950) After fat-free parenteral feedings (6/20/30–6/30/50) After fat-free parenteral feedings (6/20/30–6/30/50)
8/16/50 8/20/50 8/28/50		225 235 273										‡‡+	703	After regular diet (7/1/50-8/15/50) After fat-free parenteral feedings (8/16/50-8/26/50) After regular diet (8/27/50-11/20/50)
10/25/50		370										+		After regular diet (8/27/50-11/20/50)
11/21/50	20.7	355 155	09	36	6.	2.5	5.2	13.0	367.9	231.4	754.3	‡‡	585	After regular diet (8/27/50-11/20/50) After fat-free parenteral feedings (11/21/50-11/29/50
12/11/50**	45.6	239										‡	115	After regular dlet (11/30/50-12/15/50)
12/18/50**	50.3	255	95	37	13.2	1.1	7.7	39.8	1126.3	343.2	1724.5	000		After low fot diet (12/16/50-1/31/51) After low fot diet (12/16/50-1/31/51) After low fot diet (12/16/50-1/31/51)
/5/51	54.6	175	38	38	10.6	3.3	7.4	36.6	1035.8	330.2	1486.4	000		After low fat diet (12/16/50-1/31/51) After low fat diet (12/16/50-1/31/51)
724/51**	38.9	Ξ										000		After low fat diet (12/16/50-1/31/51) After low fat diet (12/16/50-1/31/51)
1/31/51**	35.4	124										0		After ACTH (1/26/51-1/31/51)
2/7/51**	58.6	275	101	37	14.0	4.5	8.1	46.0	1301.8	364.0	1940.8	00		After high fat diet $(2/1/51-2/15/51)$ After high fat diet $(2/1/51-2/15/51)$
3/15/51	(15/51 37.5 181 73 40 10.4 2.8 6.0 28.7 812.2 270.4	181	73	40	10.4	2.8	6.0	28.7	812.2	270.4	1263.6	0		After low fat diet (2/16/51-3/15/51)

present. However, significant hypercholesterolemia was observed on three occasions, June 20th, October 25th and November 21st, in connection with severe attacks of pancreatitis. The free to total cholesterol ratio exceeded the usual normal of 0.24 to 0.32<sup>24</sup> on every occasion that grossly lipemic four and one-half hours after a breakfast of 10 gm. of fat, 20 gm. of protein and 32 gm. of carbohydrate, and had a fatty acid concentration of 59.6 mEq./L. and a cholesterol concentration of 253 mg. per cent. Three months later a fasting specimen was even more lipemic

TABLE II
FAMILIAL SERUM LIPID STUDIES

		Total Fatty AcIds (mEq./L.)	Total Cholesterol (mg. %)	Free Cholesterol (mg. %)	Free Cholesterol Total Cholestero (%)
Mother					
11/27/50	4 hr. p.c.	20.6	191	65	36
12/22/50	fasting	12.6	185	44	24
1/12/51	fasting	12.9	173		
Father					
1/22/51	4 1/2 hr. p.c.	59.6	253		
4/19/51	fasting	85.6	338		

it was studied. Such alterations are usually regarded as evidence of liver damage<sup>25</sup> but none could be demonstrated by liver biopsy in this instance.

The phospholipid concentration, expressed as lipid phosphorus, also fell within the normal range of  $9.2 \pm 1.4$  mg. per cent<sup>24</sup> except for borderline elevations of 13.2 and 14.0 mg. on December 20th and February 14th, respectively.

In general, these findings confirm previous reports that the lipemia associated with pancreatitis is largely due to an increase in neutral fat<sup>3,4,7</sup> and that under some conditions the phospholipid and cholesterol fractions may also participate.<sup>3–7</sup> As in the present instance high free to total cholesterol ratios have been described in other cases.<sup>3,7</sup>

Ahrens and Kunkel<sup>26</sup> have suggested that the turbidity of high lipid-containing serum can be related to a low proportion of phospholipid in the total lipid mixture. This was borne out in the present case in which the increase in total lipids was due almost exclusively to neutral fat.

The same lipid pattern has been reported in idiopathic essential hyperlipemia.<sup>2,27–36</sup> This is only one of the many points of similarity between this disease and relapsing pancreatitis with lipemia.

Familial Studies. The father's serum was JANUARY, 1952

and was found to contain 85.6 mEq. of fatty acid and 338 mg. of cholesterol. (Table II.)

The mother's fasting serum was clear and had a normal lipid content. Four hours after breakfast it was slightly turbid but the fatty acid concentration was only 20.6 mEq./L., a value well within the normal postprandial range.<sup>37</sup> (Table II.)

It is clearly evident from these data that the patient's lipemia was familial in nature, which supports the view that the lipemia in such cases is a manifestation of idiopathic essential hyperlipemia rather than the result of pancreatitis.

Familial serum studies have not been carried out in the other reported cases of pancreatic lipemia, but it is significant that there was a family history of xanthomatosis in Collett and Kennedy's case.<sup>4</sup>

Relation to Attacks of Pancreatitis. The evidence is incomplete in that the serum lipids were not studied before the onset of the first attack of pancreatitis. However, in view of the earlier appearance of eruptive xanthomatosis, which may be interpreted as evidence of hyperlipemia,<sup>2</sup> it is reasonably certain that the lipemia antedated the onset of pancreatitis. Similarly in other cases of pancreatitis<sup>4,8</sup> and essential lipemia<sup>27,31,38</sup> xanthomatosis has appeared before the onset of abdominal pain.

The serum was grossly lipemic during the early phase of the severe attack of pancreatitis observed in June, 1950. Within a week the serum had cleared although active pancreatitis was still evident. Concomitantly, and even more rapidly, there was a disappearance of hypercholesterolemia, the level falling from 426 to 225 mg. per cent within twenty-four hours. (Table 1.) Similarly, during a severe attack in November, 1950, the serum cleared and the cholesterol fell to a normal level while the symptoms were still acute. A normal serum cholesterol concentration was found during an attack in August, 1950, but the serum was not examined until the fifth day so that an early hypercholesterolemia could not be excluded; unfortunately, no note was made of the presence or absence of lipemia. At the height of the attack in October, 1950, the serum was grossly lipemic and the cholesterol concentration was increased to 370 mg. per cent but the subsequent course of the lipemia during the attack was not studied.

Of special interest in connection with the relationship between lipemia and pancreatitis were the observations made during early December, 1950. On November 24th, following an attack of pancreatitis, the serum was found to be clear. During the next three weeks the serum was inspected almost daily. Gross lipemia was first detected on the morning of December 11th; and although the patient felt well at this time, typical signs and symptoms of pancreatitis developed within nine hours. The attack was of several hours' duration and subsided spontaneously. However, the next morning the serum was even more lipemic and later in the day the patient experienced another attack. It is noteworthy that no further attacks of pancreatitis occurred during the next three months of observation despite the fact that the serum remained lipemic and often contained more lipid than on December 11th.

It is evident from these observations that although hyperlipemia increased prior to the onset of pancreatitis and often decreased during the attack, the high concentration of serum lipids per se could not account for the development of pancreatitis. A similar relationship between the fluctuations in the serum lipid level and the recurrence of abdominal pain has been observed in other cases of relapsing pancreatitis8 and essential hyperlipemia. 10,32

The rapid clearing of the serum during or

immediately following an abdominal crisis has also been observed in other cases of pancreatic<sup>6</sup> and essential<sup>30,38</sup> hyperlipemia. In Holt's case<sup>30</sup> of an eleven year old girl with essential hyperlipemia it was possible to precipitate attacks of abdominal pain by raising the serum lipids to a critical level of 8 gm. per cent. Within a few hours there was usually a precipitous fall in serum lipids accompanied with enlargement of the liver and spleen and distention of the superficial abdominal veins, which led to the conclusion that the abdominal crises were due to acute distention of the liver resulting from deposition of fat. The frequent occurrence of hepatomegaly in cases of pancreatic4,7 and essential<sup>2,10,27-36,39</sup> hyperlipemia, and the demonstration of lipid-containing reticular cells in the marrow<sup>7,29b,32,35</sup> and liver<sup>32</sup> would appear to support this hypothesis. However, it is difficult to account for a sudden deposition or phagocytosis of serum lipid in an individual with longstanding hyperlipemia. Moreover, in the present case a biopsy of the liver, performed ten days after the last attack of pancreatitis and at a time when the serum was grossly lipemic, failed to reveal fatty infiltration or foam cells.

Effect of Diet. The patient was acutely ill during the first month of hospitalization and subsisted largely on parenteral injections of glucose and amino acids. The intake was low in calories and virtually fat-free resulting in a 30 pound weight loss. Concomitantly the serum cleared and there was rapid disappearance of the xanthomas. Both the initial attack of pancreatitis in 1946 and the first relapse in June, 1950, coincided with a weight gain of 15 pounds, and each of the subsequent recurrences of abdominal pain and lipemia followed a period of unrestricted dietary intake at home, suggesting that an increase in dietary fat was an important factor in producing hyperlipemia and in precipitating the relapse of pancreatitis.

When the fat intake was reduced to 20 gm. per day, there was a prompt and dramatic remission of the pancreatic symptoms, which had been present almost constantly for a period of six months, and a slower but equally impressive fall in serum lipids. In six weeks the fatty acid concentration fell from 52.8 to 29.6 mEq./L. and the cholesterol from 255 to 111 mg. per cent. (Table 1.)

The effects of a high fat diet, containing 155 gm. of fat, 90 gm. of protein and 285 gm. of carbohydrate, were studied for a two-week

period. Within a week the serum became perceptibly more lipemic and there was an increase in total fatty acid from 35.4 to 69.3 mEq./L. During the following week the level dropped slightly to 58.6 mEq. but there was an increase in cholesterol from 124 to 275 mg. per cent.

decreased by 33 mg. per cent during the first three hours and then rose to exceed the fasting level by 57 mg. per cent at eight hours. These fluctuations were due almost entirely to changes in the concentration of cholesterol esters. (Table III.) In normal subjects the administra-

TABLE III

FAT TOLERANCE TEST \*

	Total Fatty Acids (mEq./L.)	Total Cholesterol (mg.%)	Free Cholesterol (mg . %)	Free Cholesterol Total Cholesterol (%)	Lipid P (mg.%)
Fasting serum	54.4	219	93	42	12.7
3 hr. after test-meal					
serum	55.3	186	85	46	
heparinized plasma	54.6	192	91	47	11.7
8 hr. after test-meal					
serum	66.8	276	86	31	
heparinized plasma	57.0	175	74	42	

<sup>\*(</sup>a) Serum lipid concentration following a test-meal containing 59 gm. of fat, 42 gm. of carbohydrate, and 22 gm. of protein; (b) effect of <a href="In vitro">In vitro</a> heparinization on plasma lipid concentration.

(Table 1.) Despite the marked increase in lipemia there was no recurrence of pancreatitis.

When the patient was discharged from the hospital on February 15th, he was advised to resume the low fat diet containing 20 gm. of fat. He was seen again one month later on March 15th at which time he was still symptom-free. His serum was perceptibly clearer than previously, although still slightly lipemic, and the total fatty acids had fallen from 58.6 to 37.5 mEq./L. (Table I.)

These observations confirm previous reports that the lipemia and the abdominal crises can be controlled, to some extent at least, by a low fat intake, both in pancreatic<sup>8</sup> and essential<sup>2,10,27-36,39</sup> hyperlipemia.

Fat Tolerance Curve. The response of the serum lipids to a standard test meal containing 59 gm. of fat<sup>37</sup> was decidedly abnormal. In contrast to normal subjects who show a significant increase in total fatty acids at three hours, averaging 4 mEq./L.,<sup>37</sup> and a return to the initial level within six or seven hours,<sup>40</sup> the patient showed a negligible rise of only 0.9 mEq. at three hours and a precipitous rise of 12.4 mEq. at eight hours. (Table III.)

The total cholesterol, on the other hand,

tion of 80 gm. of olive oil regularly produced an increase in serum cholesterol averaging 20 mg. per cent within two to six hours. 41 However, in another study 42 a normal breakfast containing a moderate amount of fat failed to raise the total cholesterol level significantly, but there was a decrease in cholesterol esters, averaging 18 mg. per cent, during the first four hours. Although these changes were small, they occurred with such regularity as to suggest that they had significance.

Fat tolerance curves have not been reported in other cases of relapsing pancreatitis with hyperlipemia, but Bürger and Grütz<sup>39</sup> studied the response of a patient with essential lipemia to a test meal of 50 gm. of olive oil and 2.5 gm. of cholesterol. There was a precipitous fall in serum cholesterol from 686 to 363 mg. per cent in four hours and a further fall to 285 mg. per cent in eight hours. As in the present case the fall was due chiefly to a decrease in the ester fraction. Fatty acids were not determined, but there was a sharp decrease in serum lecithin from 1,740 to 368 mg. per cent during the first four hours, followed with a precipitous rise to 2,810 mg. per cent at eight hours.

Fat tolerance tests are difficult to interpret in

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terms of lipid exchange between the intestinal tract, the blood and the tissues, since the serum lipid curves obtained depend on the relative rates at which lipids are absorbed from the intestine, turned over in the liver and fat depots and utilized in the tissues. However, in view of the normal lipid content of the feces it is unlikely that the delayed rise in the fatty acid curve in the present case was due to any significant delay in fat absorption although this possibility cannot be excluded with certainty. It is more likely that fatty acids were absorbed and then retained or utilized in the liver during the first three hours. This view is supported by the recent report of Bean<sup>48</sup> that alimentary lipemia can be demonstrated in portal anastomotic veins before it becomes evident in the systemic venous circulation. Similarly, the initial fall in serum cholesterol observed at three hours might be interpreted as an indication of increased uptake by the liver although an increased rate of excretion through the biliary tree cannot be excluded.

The unusual rise in fatty acid and cholesterol at eight hours could be construed as a retention phenomenon indicating ineffectual removal of lipids by the tissues. However, indirect evidence based on radioactive tracer studies of phospholipid formation suggests that the delayed and exaggerated increase in serum lipids was due possibly to an increased output from the liver. Balfour44 showed that the increased phospholipids in a variety of hyperlipemic states, including idiopathic hyperlipemia, nephrosis and some types of liver disease, was always due to an overproduction of phospholipid, presumably in the liver. It is significant that the same type of exaggerated, sustained alimentary hyperlipemia observed in the present case has also been described in diabetes45 and nephrosis,46 two other conditions frequently associated with hyperlipemia.

Effect of Pituitary Adrenocorticotrophic Hormone (ACTH). No direct evidence of any endocrine disorder has been found in essential hyperlipemia but it has been suggested that a humoral mechanism may underlie a defect in fat turnover in the liver. 30 Insulin, thyroxin and crude extracts of the anterior lobe of the pituitary have been administered and found to be without effect on the lipemia.<sup>80</sup> Recent reports of alterations in the serum lipid pattern following the administration of cortisone<sup>47-51</sup> and ACTH<sup>47-49</sup> prompted an investigation of the effects of ACTH in the present case.

During a period of dietary restriction of fat which resulted in a marked fall in serum lipids the patient was given 525 mg. of ACTH in divided doses of 25 mg. each over a six-day period. There was a slow fall in the eosinophil count from 330 to 178 per cu. mm. in forty-eight hours. The serum which was slightly turbid at the beginning of the experiment became markedly lipemic in five days and showed a very much thicker cream layer on standing, suggesting a marked increase in neutral fat. However, the total fatty acids rose only slightly, from 29.6 to 35.4 mEq./L. There was a less significant rise in cholesterol concentration from 111 to 124 mg.

per cent. (Table 1.)

These effects of ACTH differed from those previously reported in other diseases. Adlersberg and his associates<sup>47</sup> found a significant fall in both serum cholesterol and neutral fat during the first two weeks of therapy in seriously ill patients with a variety of diseases. As in the present instance they noted a poor correlation between the degree of turbidity of serum and its neutral fat content which led them to suggest that ACTH might produce turbidity by altering the physical state of the serum lipids. Conn<sup>48</sup> also observed a fall in serum cholesterol both in normal subjects and in patients with Cushing's disease but not in cases of Addison's disease, which he attributed to increased utilization in adrenocortical steroid synthesis.

The rise in serum lipids after ACTH in the present case resembles more closely the response elicited by cortisone in experimental animals.<sup>49</sup> This effect has been ascribed to an increased mobilization of fat from the depots<sup>49</sup> and suggests the possibility that the fat depots in essential hyperlipemia are unusually responsive to endogenous adrenocortical hormone.

Effect of Heparin. A small intravenous injection of heparin will promptly abolish alimentary lipemia in both experimental animals and man. 52,58 There is evidence to suggest that this is accomplished by filtration of clustered chylomicrons from the circulation in the capillaries.<sup>54</sup> Of special interest in connection with the pathogenesis of pancreatitis in patients with essential hyperlipemia is the recent suggestion of Swank<sup>55</sup> that embolization of the capillaries by such clustered chylomicrons may lead to significant pathologic lesions.

Fifteen minutes following the intravenous injection of 50 mg. of heparin the patient's serum showed a perceptible decrease in turbidity.

However, chemical analysis revealed a decrease in fatty acids of only 5 mEq./L. and no significant change in cholesterol or phospholipid concentration. (Table IV.) The patient experienced no unusual symptoms following the injection.

To study the *in vitro* effects of heparin, simultaneously collected samples of serum and hepa-

GROSS AND MICROSCOPIC STUDY OF THE SERUM

Gross Appearance. In general there was a good correlation between the degree of turbidity and the lipid content of the serum. When the serum was lipemic, its milky appearance was detectable, almost as soon as the blood clotted, as a translucent greyish veil over the upper portion

TABLE IV

EFFECT OF AN INTRAVENOUS INJECTION OF HEPARIN (50 MG.) ON THE SERUM
LIPID CONCENTRATION

	Total Fatty Acids (mEq./L.)	Total Cholesterol (mg.%)	Free Cholesterol (mg.%)	Free Cholesterol Total Cholesterol (%)	Lipid P (mg.%)
Fasting control serum	45.6	175	66	38	10.6
Plasma 15 min. after heparin	40.6	171	79	46	10.1

rinized plasma were compared during the course of a fat tolerance test. (Table III.) The turbidity of the heparinized plasma was perceptibly less than that of its duplicate serum, especially at the height of the lipemia at eight hours. However, on chemical analysis only the eight-hour plasma showed a significantly lower lipid content than its paired serum. These results were unexpected, especially in view of previous reports that heparin has no effect on lipemic serum in vitro. 52 Although a change in the state of the lipid emulsion in plasma might account for the decrease in turbidity, it could hardly account for the significant change in lipid concentration on chemical analysis. A technical error appeared to be excluded since the analyses were carried out in duplicate and since the difference occurred not only in the fatty acid but also in the cholesterol fraction. The recent report of Swank<sup>55</sup> provides new information regarding the in vitro effects of heparin which may explain these anomalous results. Swank observed clustering of chylomicrons in vitro following heparinization, especially after a high fat diet. He also noted the disappearance of many chylomicrons and a concomitant decrease in the specific gravity of the erythrocytes, suggesting that lipid particles were being adsorbed on cell membranes. If this interpretation is correct, it is possible that the discrepancy between the lipid concentrations in serum and heparinized plasma observed at the peak of postprandial lipemia was due to a loss of adsorbed lipid in the centrifuged red cell sediment.

of the clot. After removal of the clot the character of the serum varied from an almost opaque white cream to a pale, translucent grey, depending on the total lipid content. Occasionally it had a faint pink hue, apparently due to slight hemolysis. On standing overnight in a refrigerator at 5°c. the lipids in part separated, rising to the surface as a sharply demarcated layer of dense white cream overlying a very much clearer opalescent serum. The thickness of this layer in a 10 ml. sample stored in a 15 ml. centrifuge tube varied from approximately 2 to 10 mm., depending on the total lipid concentration.

Dark-field Examination. Small drops of serum and heparinized plasma, sealed beneath thin glass cover-slips, were examined with the aid of a Spencer dark-field illuminator with built-in light source. A magnification of 950 X and maximum illumination were employed. Under these conditions the patient's lipemic serum and plasma were found to contain myriads of brightly illuminated, spherical particles with active Brownian movement in every field. By introducing erythrocytes as a reference of measurement and by comparing the lipid particles with bacteria of known size, it was estimated that they measured from 0.1 to 0.5 microns in diameter. This is somewhat smaller than the usual size of chylomicrons, which is generally stated to be 0.5 to 1.0 microns.<sup>56</sup> In some fields there were also a few larger, irregularly shaped particles which appeared to be made up of agglutinated small particles. These showed little Brownian movement. In addition to the brightly

illuminated particles there was a fine dust of barely visible, poorly illuminated, minute particles with active Brownian movement in the background. These are known to occur also in normal serum. 56,57

When lipemic serum was allowed to separate in the refrigerator, the upper cream layer was found to contain brightly illuminated, large, irregular, granular masses measuring from 20 to 100 microns in diameter. When these were set in motion by applying pressure to the coverslip, some broke up into smaller masses and into showers of individual chylomicrons while others became agglutinated to form larger masses. The lower translucent layer of such a stored sample of serum, on the other hand, showed only a few isolated chylomicrons with sluggish Brownian movement in each field.

The number of chylomicrons observed in these studies far exceeded that described in alimentary lipemia, which is usually less than 200 per field.<sup>58</sup> Differences in technic are known to influence the chylomicron count<sup>59</sup> but it is unlikely that they were responsible for the unusual number observed in the present case. The factor of storage may have been important, although it is thought not to influence the chylomicron count. 59 For technical reasons it was not possible to study these bloods immediately so that the interval between collection and darkfield examination was at least six hours and often longer. To study the effect of storage under the conditions of these experiments, a specimen of normal serum was examined at frequent intervals for a period of three days. It was found that serial counts did not differ significantly from the initial count of from 1 to 5 chylomicrons and from five to fifty smaller, poorly illuminated particles per field. Some of the patient's serum was stored in a refrigerator and re-examined at intervals for three months. The number of particles observed did not appear to change although the number of agglutinated particles increased with time.

It seems reasonably certain then that the number of chylomicrons was tremendously increased in this case. This is consistent with Moreton's report<sup>60</sup> that the turbidity of lipemic serum is related to the number of visible particles demonstrated by dark-field illumination, or measured by their Tyndall effect, and with Elke's finding<sup>57</sup> that the chylomicron count parallels the neutral fat content of the serum.

Effects of Alteration in pH and Enzyme Activity.

Elke and his associates<sup>57</sup> have presented evidence to show that the chylomicrons are negatively charged particles of neutral fat enveloped by a film of adsorbed globulin at the oil-water interface. They have shown that at the isoelectric point of globulin (pH 5.3) the particles agglutinate and cease to move. Since the possibility was considered that clustering of chylomicrons might occur in vivo in patients with lipemia, the effects of alteration in pH and enzyme activity were studied.

An equal volume of lipemic serum was added to each of a series of Michaelis veronal-buffer mixtures and the pH determined by means of a Beckman glass electrode. A small drop of each mixture was then examined microscopically under a thin cover glass, with a high-dry objective and greatly reduced illumination, at 450 x magnification. The control specimen, mixed with an equal volume of saline, showed many granules with active Brownian movement. Similar granules were observed in all specimens examined between pH and 7.0 and 10.0. However, when the pH fell below 7.0, many larger particles appeared, but it was not until the pH fell to 5.3 that large, coarse irregular clumps appeared.

Lipemic serum was mixed with an equal volume of a 2 per cent solution of a commercial, dried pancreatic extract and incubated at 37°c. for two hours. The pH of the mixture was 8.03. The enzyme solution was assayed by the same technics used for serum and was found to contain 4,180 units of amylase and 13.5 ml. of lipase. It also had considerable tryptic activity, since a 1 to 40 dilution digested the gelatin off an exposed x-ray film in two hours at 37°c. The enzyme activity of the serum itself was estimated to be 120 units of amylase and 0.7 ml. of lipase. Thus the incubated mixture contained approximately 2,260 units of amylase and 7.50 ml. of lipase, values in the range found when the patient was at the height of an attack of acute pancreatitis. Two controls were run simultaneously, one containing equal volumes of serum and saline, the other serum and boiled enzyme.

On dark-field examination both control mixtures revealed myriads of brightly illuminated particles with active Brownian movement, as previously described. In the mixture containing active enzyme, however, there were many very large, irregular, granular masses measuring up to 100 microns in diameter.

It is evident from these experiments that the

level of serum enzyme activity attained during some attacks of pancreatitis is sufficiently high to produce in vitro clustering of chylomicrons. Whether such clustering occurs in vivo and whether it can give rise to embolic phenomena are still unknown. On the other hand, the pH required to produce similar clumping was so far out of the possible physiologic range in serum that it can be excluded as a factor in the development of clustering in vivo.

Staining Properties. Since fat embolization has been reported in diabetic lipemia<sup>61,62</sup> and can be produced experimentally by the administration of ether to dogs with alimentary hyperlipemia,63 the possibility was considered that a similar phenomenon might occur in essential hyperlipemia and be of significance in the pathogenesis of pancreatitis. However, the validity of such observations has been questioned, especially in the case of diabetic lipemia, 64 on the grounds that postmortem changes in the serum lipids might produce artefacts resembling emboli. To exclude this possibility the staining properties of markedly lipemic serum stored for over three months were studied both in vitro and in nino.

On addition of a drop of Sudan III in alcohol to a drop of lipemic serum on a slide there was immediate coarse flocculation of orange-stained material easily visible to the naked eye. When the reaction was observed under the microscope, it was seen that the masses were produced by agglutination of chylomicrons, and that the granularity of these masses and their light orange stain differed markedly from the even, deep red stain of fat emboli.

Two experiments were carried out on mice weighing approximately 20 gm. In one performed under ether anesthesia the animal was allowed to bleed freely from the femoral artery for one minute and then was injected with 1.5 ml. of lipemic serum through the inferior vena cava and with 1.0 ml. through the portal vein. In the other, 1.0 ml. of lipemic serum was injected into the tail vein of an unanesthetized animal. In both experiments the animals were sacrificed immediately following completion of the injection, and the lungs, kidneys and liver were removed for fixation in 10 per cent formalin. Following fixation frozen sections were stained with Sudan III. The results were similar in both experiments, except that the changes in the vessels, especially in the kidneys and liver, were more marked where the larger injection had

been used. Many of the medium- and large-sized vessels in all three tissues contained pale, orange-stained, granular material which filled the lumen, and in a few there were, in addition, brightly stained, deep red fat droplets measuring from 5 to 40 microns in diameter. Similar brightly stained fat globules were observed in some of the pulmonary capillaries and hepatic sinusoids but none were found in the glomeruli of the kidneys. In none of the sections studied did the brightly stained fat conform to the shape of the vessels, as in fat embolism, and it was the opinion of an experienced pathologist who was shown the sections that the findings could not be mistaken for those of fat embolism.

#### URINE LIPID STUDIES

The frequent occurrence of fat droplets in the urine following traumatic fat embolism and its diagnostic importance were first emphasized by Scriba<sup>65</sup> in 1880. Using the technic described by Scuderi66 fat droplets were sought for in the urine on ten occasions during experimental periods when it was thought that an attack of pancreatitis might be precipitated. The experimental procedures employed included raising the serum lipids by means of a high-fat diet and ACTH, the production of mild acidosis with large doses of ammonium chloride and stimulation of pancreatic secretion by means of secretin. No fat droplets were demonstrated in the urine but neither was an abdominal crisis precipitated in any of these experiments.

Although these results were inconclusive, it would be worth looking for fat in the urine in future cases, especially during an attack of pancreatitis and for several days thereafter. Scriba<sup>65</sup> found that in traumatic fat embolism fat appeared in the urine two to four days after injury and often reappeared eight to ten days later.

#### PANCREATIC FUNCTION STUDIES

Serum Enzymes. The serum amylase level was increased significantly during each major attack of pancreatitis observed but it usually fell to normal before the symptoms had fully subsided. (Table v.) During symptom-free periods the level was always within the normal range. Serum lipase activity was measured less frequently but in general it paralleled that of amylase. (Table v.) However, on one occasion, November 29, 1950, when the patient experienced a peculiar attack of shock without abdominal pain following an infusion of saline and glucose, there was

a slight rise in lipase activity to 1.9 ml., and a further increase to 2.2 ml. a few days later, without a concomitant increase in serum amylase activity. As in the case of amylase, serum lipase activity was normal during symptom-free periods.

Secretin Test. There was no significant in-

TABLE V SERUM ENZYME STUDIES

	Amylase* (units)	Lipase† (ml.)	Pancreatic Pain
6/20/50	1225		Severe, constant
6/21/50	395		Severe, constant
6/29/50	193		Moderate, Intermittent
6/29/50	201		Moderate, Intermittent
7/3/50	211		Moderate, Intermittent
7/6/50	182		Moderate, Intermittent
8/15/50	555		Moderate, constant
8/16/50	703		Moderate, constant
8/18/50	1825		Moderate, constant
8/22/50	2160		Moderate, constant
8/24/50	1845		Mild, intermittent
8/28/50	275	2.0	Mild, Intermittent
9/4/50	195		
10/20/50	125	0.5	Moderate, constant
11/21/50	585	7.4	Severe, constant
11/24/50	130	1.1	Severe, constant
11/29/50	132	1.9	Vasomotor collapse, no pain
12/2/50		2.2	None
12/11/50	115	1.3	Mild, Intermittent
12/12/50	100	0.9	Mild, intermittent
12/14/50	132		None
2/9/51	115	0.5	None
2/12/51	120		None
2/13/51	95		None

<sup>\*</sup>Normal values: less than 200 units; Clark method. 77

crease in serum amylase or lipase activity after an intravenous injection of 58 units of secretin.

	Amylase	Lipase
Fasting	115	0.5
½ hour		
1 hour		0.3
2 hours	. 105	0.4

Pancreatic Secretion. The duodenal contents were aspirated by means of a Miller-Abbott tube one-half hour after an intravenous injection of 58 units of secretin and were found to have an amylase activity of 685 units. A control sample obtained from a normal subject under the same conditions contained 640 units.

Fecal Tryptic Activity. A suspension of feces incubated at 37°c. digested the gelatin off a strip of exposed x-ray film in one hour. A control specimen behaved in a similar manner.

Fecal Nitrogen and Fat Content. On a diet containing 90 gm. of protein, 155 gm. of fat and 285 gm, of carbohydrate the patient excreted 8.92 gm. of fat and 2.47 gm. of nitrogen per day. The value for fat was well within the normal range but that for nitrogen was slightly above the normal range of 1 to 2 gm. a day.

Glucose Tolerance Test. Normal curves were obtained after oral and intravenous glucose administration. On September 4, 1950, the fasting blood sugar was 100 mg.; one-half hour after 50 gm. of glucose orally 85 mg.; two hours after, 105 mg. per cent. On October 26, 1950, the fasting blood sugar was 75 mg.; one hour after 25 gm. of glucose intravenously 80 mg. and two hours after, 65 mg. per cent. On February 15, 1951, the fasting blood sugar was 78 mg.; one-half hour after 50 gm. of glucose orally 177 mg. and two hours after, 110 mg. per cent.

X-ray Studies. Flat films of the abdomen failed to reveal any evidence of calcification in the region of the pancreas and the contour of the duodenal loop appeared normal following a barium meal.

It was concluded from these studies that, except for a borderline elevation in fecal nitrogen excretion, there was no evidence of pancreatic dysfunction during symptom-free periods.

#### COMMENTS

The familial nature of the lipemia in cases of relapsing pancreatitis, its persistence during

<sup>†</sup>Normal values: less than 1.5 ml.; Cherry-Crandall method.

symptom-free periods without evidence of pancreatic dysfunction, and the appearance of xanthomas before the onset of abdominal symptoms are highly suggestive indications that pancreatitis is the result rather than the cause of lipemia when these two conditions occur together. Moreover, the clinical and laboratory features in such cases so closely resemble those of essential hyperlipemia as to make it reasonably certain that the two diseases are identical. In Table vi are summarized the essential data of all published cases in both categories. Especially significant are the striking similarities in age distribution, family history, the recurrent nature of the abdominal pain, the serum lipid pattern, the response to a low fat diet and the occurrence of hepatosplenomegaly, xanthomas and lipemia retinalis.

With the exception of Poulsen,<sup>7</sup> other authors have regarded these two conditions as unrelated entities having similar clinical features but very different etiologies. This opinion has been based on the stated failure of serum and urine amylase to increase during the abdominal crises of essential lipemia, the absence of pancreatitic lesions in the only such case to come to autopsy<sup>28</sup> and on certain experimental evidence suggesting that the pancreas plays a role in fat metabolism.

Tests of serum and urine enzyme activity are, at best, unreliable criteria for excluding pancreatitis, since the results are frequently normal in that disease. 13,14 However, they were not carried out at all in thirteen of the nineteen reported cases of essential lipemia with abdominal pain (Table vi) so that pancreatitis was by no means excluded. Moreover, in two of the eleven cases reported as pancreatitis<sup>5,6d</sup> the diagnosis rested on the clinical features alone. A third case, reported by Bernhard<sup>10</sup> as an example of lipemia of undetermined etiology, has also been included in the pancreatitis group by some authors<sup>2</sup> although the urine diastase was normal and the character of the pain did not suggest pancreatitis. In Holt's case, 30 on the other hand, the diagnosis of pancreatitis was excluded and the pain attributed to distention of the liver, despite the fact that earlier in the course of the disease free fluid was found in the abdomen and thought to be due to pancreatitis. It is apparent from these observations that in the past the differentiation between pancreatitis with lipemia and essential lipemia with abdominal pain has been based more often on clinical criteria than on objective evidence.

Although it is suggested that pancreatitis is a manifestation of essential lipemia, it is not implied that all the abdominal crises in the latter condition are necessarily due to pancreatitis. The significance of this paradoxic statement will become apparent in the discussion on pathogenesis.

The importance of the postmortem findings in Chapman and Kinney's case28 with respect to the distinction between essential and pancreatic lipemia has been overemphasized. Although no pancreatic lesions were found in this twenty-one month old infant with lipemia, it had not yet experienced any abdominal crises and had died of unknown causes following an upper respiratory infection. Not all cases of essential lipemia develop pain2,33a,39 and even in cases with pancreatitis there may be long symptom-free periods despite the persistence of marked lipemia.76,8 In the present case the patient's father had marked lipemia in middle age, yet had never experienced abdominal symptoms.

The experimental evidence implicating the pancreas in fat metabolism has already been reviewed, and it was pointed out that it offers no support for the hypothesis that pancreatic disease produces hyperlipemia, whatever other effects it may have elsewhere.

As for the production of pancreatitis by lipemia there are several possible mechanisms. Lipemia might provoke pancreatitis by producing xanthomatous lesions in the pancreas, by producing atherosclerotic vascular lesions or by giving rise to fat emboli. The pancreatic nodules found in Wijnhausen's case8 were necrotic and contained xanthoma cells in their walls. It is possible that the nodules represented degenerated xanthomas and were responsible for the attacks of relapsing pancreatitis. However, it is more likely, in view of the well known tendency for xanthoma cells to localize at sites of inflammation in hypercholesterolemic states,70 that the nodules were the result of a focal necrotizing inflammatory process and that the xanthomatous infiltration was secondary.

In view of Moreton's work<sup>60</sup> on the relationship between high chylomicron counts and the development of atherosclerosis, the unusual chylomicronemia in the present case lends support to the possibility that the pancreatitis may be the result of such vascular lesions in lipemic states. However, no other evidence of vascular disease has been found in such cases nor has

pancreatitis been described in essential xanthomatosis, a disease characterized by hypercholesterolemia and frequently associated with atherosclerotic vascular lesions.

The last possibility that the abdominal crises of essential lipemia are due to embolization of agglutinated serum lipid particles appears to be the most promising, but still lacks direct proof. However, it has the support of an impressive body of circumstantial evidence. (1) Fat

embolism is known to occur in diabetic<sup>61,62</sup> and in other types<sup>63,71</sup> of lipemia. In the remarkable case reported by Bantin<sup>62</sup> the emboli were actually observed moving through the retinal vessels during life. (2) Fat emboli have been described in the pancreas<sup>64,72,73</sup> and occasionally produce marked interstitial edema.<sup>72</sup> (3) In several cases of essential lipemia and pancreatitis there have been clinical features to suggest disseminated embolic phenomena in other organs.

TABLE VI

## COMPARISON OF CLINICAL AND LABORATORY FEATURES IN PUBLISHED CASES\* OF PANCREATIC AND ESSENTIAL HYPER-

	Pancr	eatic Lipemia	Essenti	ial Hyperlipemia
	No.	Reference	No.	Reference
Total Number			20	0.10.07.01.00
	11	3-8, R.K.†	20	2,10,27-36,38, 39,67
Sex		00111		2,10,27-29,31-36
Male	8	3-5, 6c, 6d, 7b, 8, R.K.	18	38,39
Female	3	7a,6a,6b	2	30,67
Age at onset‡			•	07 01 04 07 00 47
under 20 yr.	5	4, 6a, 7, R.K		27-31, 34, 36, 39, 67
20-30 yr.	2	5,8	6	2b, 2c, 10, 33b, 35, 38
31-40 yr.	3	3,6b,6d	2	2d, 33a
over 40 yr.	0		3	20, 32, 33c
unknown	1	6c	-	
Family history				
serum tested§	2	7, R.K.	6	28-30, 33a, 35, 39
lipemia present	2	7, R.K.	2	29, 30
pancreatitis	1	7	0	
xanthomatosis	1	4	0	
Abdominal pain				
present	11	3-8, R.K.	12	10, 27, 29-32, 33b, 33c, 34-36, 38
Intermittent	10	4-8,R.K.	11	10, 29-32, 33b, 33c, 34-36, 38
Xanthomas of skin				
present before first ab-	4	4,6c,8,R.K	. 8	2a, 2b, 2d, 27, 28, 31, 38, 39
dominal crisis	3	4,8,R.K.	3	27, 31, 38
subsided on low fat diet	2	8, R.K.	5	2a, 2d, 27, 28, 39
Lipemia retinalis	1	7b	9	2ь, 27-30, 32, 35,
				36, 39
Hepatomegaly	3	4,7	16	2a, 2c, 10, 27-36, 39
Splenomegaly	2	4,7b	14	2a, 1J, 27-31, 33b, 33c, 34-36, 39, 67

"See footnote first page of article. Thannhouser2 reported four cases, and Movitt et al. 33 three cases of essential hyperlipemia. The letters a, b, c and d have been assigned to each of these cases but are used only when all cases reported by each author fail to fall into the same category. Harslöf 29 mentions the findings in two siblings, but these have been omitted because too few details are available for analysis. Bürger and Grütz's second case 39 has been omitted because it had chronic jaundice and probably does not belong in the essential hyperlipemia group. Herbert's case 69 has also been omitted for the same reason. Goodman's case 68 is not included because more complete data are available in the later report of Chapman et al. 28

†R.K., present case.

‡Age at which abdominal symptoms, lipemia or xanthomatosis first became evident.

§These data are incomplete in that not all members of the family were tested in every instance.

TABLE VI (Continued)

			Essen	tial Hyperlipemia
		. Reference	No.	
Serum lipias				
total lipids measured	5	4, 5, 7, R.K.	18	2, 27-36, 39, 67
total lipids increased	5	4,5,7,R.K.	18	2, 27-36, 39,67
	4	4,7,R.K.	14	
neutral fat measured				2, 27-29, 31-34, 36
neutral fat increased	4	4,7,R.K.	14	2, 27-29, 31-34, 36
phospholipids measured	4	4,7,R.K.	18	2, 27-36, 39, 67
phospholipids increased	4	4,7,R.K.	14	2, 27-30, 33, 34, 36, 39
cholesterol measured	11	3-8, R.K.	20	2,10,27-36,38,39,67
cholesterol increased	11	3-8, R.K.	18	2a, 2b, 2d, 10, 27-36, 38, 3
lipemia between attacks		,		22,22,22,10,0
tested	5	4,7,8, R.K.	11	10,27,29-32,33b, 33c,34-36
	-	470 DV	10	
present	5	4,7,8,R.K.	10	27,29-32,33b,33c, 34-36
lipemia reduced during or				
following abdominal pain effect of low fat diet	7	3, 4, 6, R.K.	3	10, 30, 38
tested	4	4, 5, 8, R.K.	16	2a, 2c, 2d, 10, 27-32,
lesied	7	., 0, 0, 1, 1, 1, 1		33c, 34-36, 38, 39
1 110	2	4004	14	
reduced lipemia	3	4,8,R.K.	16	2a,2c,2d,10,27-32, 33c,34-36,38,39
Urine or serum amylase				
tested	5	3,6a,7,R.K.	7	28,30,31,33a,33b,35,38
Increased	5	3,6a,7, R.K.	0	
Serum Ilpase				
	,	D 1/	4	00 221 25 20
tested	1	R.K.	4	28,33b,35,39
Increased	1	R.K.	0	
decreased	0		2	28,39
Diagnosis of pancreatitis				
confirmed surgically	7	4,6a-c,7a,8,	1	30 (?)
commiled sorgically	,		,	30 (1)
suggested or ex-		R.K.		
cluded on clinical				
_	2	E 4.1	6	10,27,29,32,34,36
criteria only	2	5,6d	0	10,27,27,32,34,00
Blood sugar				
tested	8	3-5,6a,7,8, R.K.	12	2a, 2b, 2d, 27-31, 33, 67
Increased	3	3,6a,8	2	2a, 2d
Glycosuria present	1	8	3	2a,2d,31
Liver function				
tested	3	4,7a, R.K.	5	10,31,33
abnormal	2	4,7a	0	-,-,
	-	7,7 4	9	
Liver Biopsy				
performed	1	R.K.	2	32,33a
lipoidal cells			-	,
present	0		2	32,33a
•	0		2	32,330
Bone marrow biopsy	_	~		00 00 00 05
performed	2	7	6	29,32,33,35
lipoidal cells				
present	2	7	2	32,35
Skin biopsy				
performed	1	R.K.	2	28,39
	0			
lipoidal cells present	1	R.K.	2	28,39

Thus there are reports of transient paralysis, 7b epileptiform seizures, 5 unexplained gastrointestinal hemorrhage 33, 35 and, in the present case, vasomotor collapse without pain. (4) Similar abdominal crises are known to occur in other lipemic states characterized by a high neutral

fat, as in diabetes<sup>74</sup> and nephrosis.<sup>75</sup> (5) Two curious features of essential lipemia, the rapid clearing of the serum and the appearance of hepatomegaly during abdominal crises are entirely consistent with what might be expected in fat embolization. The previously cited experi-

ments with heparin illustrate the manner in which clustering of chylomicrons can reduce lipemia and autopsy studies provide evidence that fat embolization may produce acute congestion of the liver.<sup>65,72</sup>

It would be unusual if the pancreas were the only organ to be involved in such an embolic process. Certainly, the predominance of pain in the right upper quadrant and the associated tenderness and hepatomegaly in some cases<sup>10,30,33c,38s</sup> suggest that the liver is at times the principal organ involved, and there is no reason why involvement of other viscera could

not give rise to symptoms.

Little is known about the factors which precipitate the abdominal crises in lipemia. Certainly a high level of neutral fat in the serum is important, but it does not appear to be the decisive factor in all cases. Although Holt and his associates<sup>30</sup> could provoke attacks of abdominal pain by raising the serum lipids to a critical level, it was not possible to do so in the present case either by dietary means or with ACTH. It is highly probable that the tendency toward clustering increases with the chylomicron count. However, it was shown that very high counts may occur without evident clustering or signs of embolization. The predominance of symptoms in the abdomen suggested that alterations in serum pH or enzyme activity related to the process of digestion might result in agglutination and embolization of lipid particles. However, it was shown that the pH required to bring about such a change was well outside the physiologic range and that the enzyme concentration required far exceeded that attained in the serum during normal digestion or following secretin stimulation. In view of the remarkable effects of heparin on lipemia, the possibility must be considered that heparin or heparin-like compounds may gain entrance to the circulation, at least locally in such organs as the liver and pancreas, to produce clustering and embolization. In the present experiment heparin did not provoke an abdominal crisis although some lipid appeared to have been removed from the circulation. Possibly a larger dose would have been more effective. Obviously, further studies are needed to clarify the relationship between the physical state of the serum lipids and the occurrence of pancreatitis and other abdominal crises in cases of lipemia.

The basic defect underlying the high level of serum lipids in essential hyperlipemia is still unknown. Hyper-alimentation and an exaggerated alimentary hyperlipemia can be excluded since complete exclusion of fat from the diet fails to overcome the lipemia, <sup>30</sup> although it may reduce it; nor does there appear to be any defect in the utilization of fat since the respiratory quotient falls in a normal manner following the administration of fat, <sup>36</sup> and there is no impairment of nutrition.

The low serum lipase levels found in some cases<sup>28,39</sup> have been cited in support of the hypothesis that there is an impairment of fat deposition in the tissues related to a similar decrease in tissue enzyme activity.<sup>28</sup> However, normal serum values have been reported in other cases<sup>33b,35</sup> and in the present instance serial lipase and phosphatase determinations revealed normal values during symptom-free periods even when the serum was grossly lipemic. Moreover, too little is known about the relationships between tissue or serum enzyme activity and the basic chemical reactions involved in fat deposition to warrant any conclusions based on such serum enzyme studies.

It has been suggested that the lipemia may be related to a fault in fat transport across congenitally anomalous vascular membranes.2 Although this possibility cannot be excluded, the unusual delayed rise in serum lipids noted in the fat tolerance test and the failure of a virtually fat-free diet to abolish lipemia are strongly against any type of retention phenomenon. The same objections may be raised against the theory that there is a defective mechanism for fat removal in the liver. Although the abnormal ratio of free to total cholesterol in the serum and the presence of hepatomegaly in some cases suggests some alteration in the liver, no significant abnormalities could be demonstrated either histologically or by function tests in the present case. Moreover, it is possible that the increased proportion of free cholesterol in the serum of such cases is a reflection of an abnormally rapid turnover of lipids in the liver rather than evidence of liver damage. The marked increase in the ratio of free to total cholesterol from 0.45 to 0.86 during the fat tolerance test in Brüger and Grütz's case<sup>39</sup> would favor such a possibility.

What few facts are known about essential lipemia would appear to be best explained on the basis of an increased lipid turnover in both the liver and fat depots. These include the exaggerated but delayed alimentary lipemia, the

evidence of an increased phospholipid turnover based on traces studies<sup>44</sup> and the unusual lipemic response to ACTH under conditions of marked restriction of dietary fat. Its familial character suggests further that the lipemia may be the result of a constitutionally determined over-responsiveness of the liver and fat depots to the normal stimuli which govern fat mobilization.

#### SUMMARY

A case of relapsing pancreatitis with hyperlipemia and xanthomatosis was investigated. Evidence was obtained which indicated that the hyperlipemia was familial in nature, that it antedated the onset of abdominal pain and that its severity, which could be controlled by dietary regulation, was an important factor in precipitating the relapses of pancreatitis. It was concluded that when relapsing pancreatitis and hyperlipemia occur together, pancreatitis is the result rather than the cause of the hyperlipemia, and that both are manifestations of the hereditary disorder known as essential hyperlipemia.

Experiments designed to elucidate the mechanisms underlying the pathogenesis of pancreatitis in such cases were inconclusive. However, evidence was reviewed which suggests that the relapsing pancreatitis and other abdominal crises which occur in essential hyperlipemia may be the result of alterations in the physical state of the serum lipids leading to vascular occlusions by clumped lipid particles.

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## Antithrombin Titer in Acute Pancreatitis\*

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In a previous communication we have recorded the experimental data of trypsin-induced alterations in antithrombin levels in dogs. Additional features included a shock-like state, hemorrhagic phenomena, actual necrotizing vasculitis, alterations in the clotting

duce contamination by tissue fluids the initial 3 cc. of blood drawn into the syringe was discarded. The sample to be analyzed was received into a second syringe containing the anticoagulant. In this manner nine volumes of blood were added to one volume of 1.85 per cent sodium

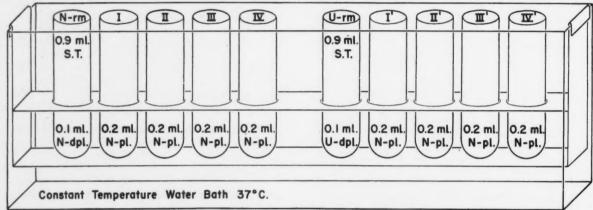


Fig. 1. N-rm, reaction mixture consisting of 0.9 ml. standardized thrombin plus 0.1 ml. of normal defibrinated plasma; U-rm, reaction mixture consisting of 0.9 ml. of standardized thrombin plus 0.1 ml. of unknown defibrinated plasma; S. T., standardized thrombin; N-pl., normal plasma; N-dpl., normal defibrinated plasma; U-dpl., unknown defibrinated plasma; N-rm, (reaction mixture of S. T. and N-dpl.) is incubated at 37°c.; then 0.1 ml. of N-rm is added to 0.2 ml. of N-pl. at one, five, ten and fifteen-minute intervals, respectively, and tested for clotting time (I, II, III and IV); U-rm, (reaction mixture of S. T. and U-dpl.) is incubated at 37°c; then 0.1 ml. of U-rm is added to 0.2 ml. of N-pl. at one, five, ten and fifteen-minute intervals, respectively, and tested for clotting time (I¹, II¹, III¹ and IV¹).

mechanism<sup>7,8,9,11</sup> and blood chemical changes consisting of hyperglycemia, elevated amylase and hypocalcemia.<sup>10</sup> (Fig. 1.) It was apparent, therefore, that several features of the syndrome of acute pancreatitis had been reproduced. Because of a remarkable and consistently demonstrable rise in antithrombin titer under the experimentally-induced conditions we decided to study the antithrombin levels in proven clinical cases of acute pancreatitis.

#### **METHODS**

The present report is based upon data obtained from the determination of the antithrombin level in a series of 659 patients. Blood was obtained by venipuncture. In order to recitrate. After centrifugation at 2,000 r.p.m. for fifteen minutes the plasma was carefully removed from the cellular elements and a determination was either immediately carried out or the plasma was refrigerated until analyzed. The normal control plasmas were collected and refrigerated until they were measured at the same time as the unknown samples.

Plasma Antithrombin Test. The procedure represents a modification of the method of Quick. 12 According to Quick, plasma antithrombin levels correlate with the clotting time of defibrinated plasma plus thrombin plus fibrinogen aliquots. This complex coagulation system, however, reflects alterations in antithrombin and other variables. These variables

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include prothrombin concentration, the activity of prothrombin conversion factors, possible deterioration of thrombin in solution, changes in the temperature and pH of thrombin in solution, types and concentration of anticoagulant employed, and the source and age of the fibrinogen used.

This clotting system may denote antithrombin alterations when the technic rigidly controls extraneous variables. With this in mind, we modified Quick's technic as follows: (1) The thrombin solution is standardized prior to each day's determinations. (2) Thrombin deterioration is prevented by regulating temperature and pH changes. (3) The quantity of thrombin is constant. (4) Fresh plasma, obtained from normal persons, is the source of fibrinogen. (5) Normal controls are run simultaneously with each unknown sample.

Standardization of Thrombin. Two milliliters of isotonic saline are injected into a 1000 unit vial of Parke, Davis topical thrombin; 0.25 ml. of this thrombin solution is introduced into a 50 ml. flask containing 20 ml. of isotonic saline. The flask is carefully surrounded by ice in a small beaker (the temperature is maintained at 2°c.) and allowed to stand for fifteen minutes before used in the procedure. One-tenth milliliter of this thrombin solution is added to  $\frac{2}{10}$  ml. of normal plasma and a clotting time is determined. If the clotting time is in a fifteen- to sixteen-second range, the thrombin solution is satisfactory. Usually this preliminary clotting time is in a twelve- to fifteen-second range. Isotonic saline in 5 ml. quantities are then added to the thrombin solution until the mixture of  $\frac{1}{10}$  ml. of thrombin to  $\frac{2}{10}$  ml. of normal plasma yields a clotting time in the fifteen- to sixteen-second range.

Unit of Antithrombin. A unit of antithrombin is defined as that amount present in a  $\frac{2}{10}$  ml. aliquot of plasma which, when added to  $\frac{1}{10}$  ml. of standardized thrombin, forms a clot in fifteen seconds.

Use of Standardized Thrombin in the Test. Fourtenths milliliter of the standardized thrombin solution are added to 1 ml. of the patient's plasma. Two to four minutes later the formed clot is removed. One-tenth milliliter of the resultant defibrinated plasma is added to  $\frac{9}{10}$  ml. of freshly standardized thrombin. This 1 ml. specimen, a mixture of defibrinated plasma and thrombin, is incubated in a water bath at  $37^{\circ}$ c. along with a series of test tubes containing

2/10 ml. of normal plasma. At intervals of one, five, ten and fifteen minutes 1/10 ml. of this incubated thrombin and defibrinated plasma solution is added to one of the 2/10 ml. incubated samples containing normal plasma, and a clotting time is taken. A normal control is run on normal plasma together with each unknown determination. A "normal" result is recorded when the clotting time of the control and unknown samples are either identical or show minimal variation. (Fig. 1.)

A standard normal is defined as one containing a total antithrombin range of 1 to 6 units and in which clotting occurs within a prescribed range at each incubation period.

STANDARD NORMAL ANTITHROMBIN TITER

Incubation Time (min.)	Clotting Time (sec.)	Antithrombin (units)
1	15–16	1
5	22-25	1.5
10	40-50	2.5-3.2
15	70-90	4.8-6

"Positive" Result. An abnormal or a "positive" result is recorded when the clotting time of the unknown sample is at least 100 per cent greater than that of the normal control at the five-minute incubation period. Furthermore, the clotting time of the unknown sample must be greater than 300 seconds at the fifteenminute incubation period.

In terms of antithrombin units there should be a minimum of twenty antithrombin units demonstrable not later than the fifteen-minute incubation period. During the course of this investigation it was not unusual to observe twenty units or more of antithrombin in patients with acute pancreatitis as early as the five-minute period of incubation. In all determinations the end point is reached when the wire loop first draws a thin fibrin strand above the incubated mixture.

#### PROCEDURE

During the course of this investigation the antithrombin titer was determined in 659 patients. The patients were subdivided into four groups, namely, (1) 150 "normal controls" consisting of healthy medical students, interns and laboratory technicians; (2) 150 consecutive ambulatory patients visiting the office of an

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Table 1 comparison of the antithrombin activity in the plasma of 659 patients\*

				Patient	Groups			
Incubation Period (min.)	Normal Con 150 Case		Ambulato 150 Case		"Acute Surg Abdome 304 Case	n	Acute Pancreatiti 55 Cases	s
	Clotting Time (sec.)	No. of Cases	Clotting Time (sec.)	No. of Cases	Clotting Time (sec.)	No. of Cases	Clotting Time (sec.)	No. of
1	15 16 17 Mean 16.4	36 41 73	15 16 17 25 Mean 15.9	80 31 36 3	15 16 17 25 26 Mean 16.2	54 214 26 8 2	16 neg. 24 25 26 27 28 29 30 Mean 27.6	5 9 2 8 2 4 15 10
5	27 28 29 30 Mean 28.3	42 81 14 13	20 21 22 23 24 51 53 57 Mean 22.4	9 19 94 15 10 1	29 30 31 32 34 68 70 Mean 32.4	44 68 37 91 54 3 7	28 30 neg. 70 72 75 80  Mean 73.6	2 3 7 26 14 3
10	56 57 58 59 Mean 58.1	19 41 74 16	54 55 56 57 120 or over	20 26 82 19 3	45 48 49 50 51 52 53 54 200 or over Mean 52.7	7 20 11 49 61 103 14 29	47 51 53 205 210 220 260 320 5 min. or over Mean 318.4	1 2 2 7 9 11 10 11 2
15	105 110 120 130 Mean 118.3	10 75 43 22	105 110 120 130 260 or over Mean 115.9	47 23 69 8 3	100 105 110 115 120 5 min. or over Mean 106.3	75 124 46 10 39 10	102 104 109 114 119 5 min. or over. Mean 5 min. or over	1 1 1 1 1 50
20	150 160 170 180 190 Mean 178.5	17 9 11 91 22	150 160 170 180 190 5 min. or over Mean 171.3	14 31 85 6 11 3	150 160 170 180 190 5 min. or over Mean 180.3	25 44 74 110 41 10	172 173 175 184 195 5 min. or over Mean 5 min. or over	1 1 1 1 1 50
24	240 or over 300 or over Mean 300 or over	30 118	200 or over 240 or over 300 or over Mean 300 or over	8 32 110	200 or over 240 or over 300 or over Mean 300 or over	7 41 256	220 240 300 or over 300 or over Mean 5 min. or over	1 1 3 50

<sup>\*</sup>neg. = negative

internist (I. I.); (3) 304 cases of the "acute abdomen" chosen at random from the wards of several municipal hospitals (in this group were included cases of myocardial infarction presenting acute abdominal manifestations, Table II); (4) fifty-five cases of acute pancreatitis

In fifty of the fifty-five patients (91 per cent) with acute pancreatitis a strongly positive result was obtained. The antithrombin titer was performed at intervals varying from three hours to three days following the onset of symptoms and in several cases positive findings were ob-

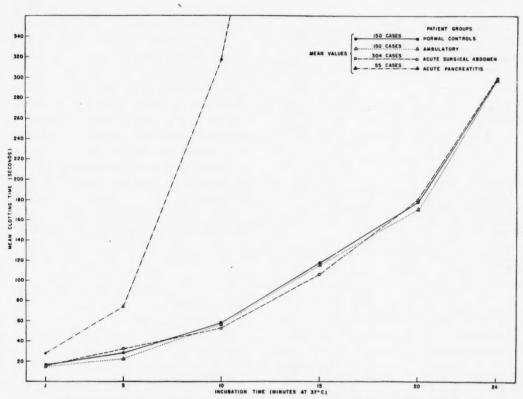


Fig. 2. Comparison of the antithrombin activity in the plasma of 659 patients.

selected from the surgical service of various hospitals in the City of New York. The clinical diagnosis of acute pancreatitis was based upon one or more of the following factors: a consistent clinical history and course associated with elevated amylase levels, characteristic operative findings and postmortem studies.

Each drawn citrated blood sample was immediately packed in ice until tested.

#### RESULTS

No elevation in antithrombin titer was observed in the control group of 150 patients. Three of the 150 ambulatory patients of the second group yielded distinct elevations in antithrombin titer (2 per cent). In 97.3 per cent of the third group of 304 patients diagnosed "acute surgical abdomen" the antithrombin titers were entirely negative. (Table I.)

tained as long as five days after the onset of symptoms. The criteria for this diagnosis included an elevation in the amylase level and compatible findings on clinical history, operation and/or autopsy.

#### COMMENTS

The magnitude of antithrombin elevation in acute pancreatitis is illustrated most clearly by an analysis of the antithrombin levels at comparable incubation periods in the four groups under investigation. (Fig. 2 and Table I.)

After one minute of incubation the mean clotting time was 16.4 seconds for the normal controls, 15.9 seconds for the ambulatory group, 16.2 seconds for patients with an "acute abdomen" and 27.6 seconds for the patients with pancreatitis. (Table I.)

The range of clotting time in each group was

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as follows: fifteen to seventeen seconds in the "normal" group; fifteen to twenty-five seconds in the ambulatory group (the three "positives" clotted at twenty-five seconds); fifteen to twenty-six seconds in subjects with an "acute abdomen" (ten "positive" clotted close to the

Table II
RESULTS OF THE ANTITHROMBIN TEST IN FIFTY-FIVE PATIENTS WITH ACUTE PANCREATITIS AND IN 304 ACUTE
SURGICAL ABDOMINAL DISEASES

Clinical Diagnosis	No. of Cases	Posi- tive	Nega- tive	Per- cent- age Posi- tive
Acute pancreatitis	55	50	5	91
Coronary occlusion	29	0	29	0
Acute appendicitis	39	0	39	0
Acute cholecystitis	39	3	36	7.7
Perforated peptic ulcer		1	8	11.1
Intestinal obstruction	14	0	14	0
Acute salpingitis	53	0	53	0
Acute alcoholic gastritis		4	12	25
Gastric cancer with he-				
matemesis	8	0	8	0
Acute salpingo-oophoritis	32	0	32	0
Empyema of gallbladder.		2	13	13.3
Twisted ovarian cyst		0	12	0
Strangulated inguinal her-				
nia	1	0	10	0
Acute diverticulitis		0	15	0
Mesenteric thrombosis	1	0	7	0
Perforation of gallbladder	1	0	6	0

twenty-six second mark); and sixteen to thirty seconds in subjects with acute pancreatitis. The majority of the five "negatives" in the latter group had clotting times of or about sixteen seconds. Almost all of the fifty positive tests showed clotting near the thirty-second mark.

The differences between the subjects with acute pancreatitis and those in the three control groups are more noticeable at only ten minutes of incubation. The three control groups showed mean clotting times of 58.1, 56.8 and 52.7 seconds, respectively. The mean clotting time for the control groups after the same period of incubation was 55.5 seconds. (Table I.)

In the same ten-minute incubation period the mean clotting time in acute pancreatitis was 318.4 seconds. This represents an increase of approximately 600 per cent. (Table I.)

Similarly, sharp elevations in antithrombin

were noted in patients with pancreatitis as compared with subjects in the control groups in each of the remaining incubation periods. (Table 1, Fig. 2.)

It is therefore apparent that the elevations in the antithrombin level in patients with acute pancreatitis above those of the control groups are of sufficient magnitude to assume diagnostic importance.

Three patients (2 per cent) in the ambulatory group showed an elevation in antithrombin titer. A summary of a typical case follows:

A forty-eight year old white housewife complained of epigastric pain for about two weeks. The pain was aggravated by eating, radiated toward the left hypochondrium and then to the lower dorsal vertebrae. In 1946 a diagnosis of gallbladder disease was made by her family physician and since that time a fat-free diet was scrupulously followed and she had had upper abdominal pain only occasionally. During the past two weeks, however, she had had frequent epigastric pain. Physical examination elicited marked epigastric tenderness and deep tenderness in the left hypochondrium. Laboratory data were as follows: blood sugar 90 mg per cent, cholesterol 190, cephalin flocculation negative, urinalysis was negative, non-protein nitrogen 12 gm. per cent, albumin 4.6 gm., globulin 2.1 gm., serum amylase 364 units (Somogyi).

The results of the antithrombin titer determination were as follows:

	Cl	otting Time	(sec.)
Incubation (min.)	Normal Control	Patient	Antithrombin (units) Patient
1	16	29	2
5	28	74	5
10	57	214	14.8
15	110	over 300	over 20.0
20	190	over 300	over 20.0

The patient was then hospitalized and following administration of secretin the amylase rose to 410 units (Somogyi). A diagnosis was made of chronic relapsing pancreatitis.

Ten of the 304 patients with an "acute surgical abdomen" (3 per cent) yielded positive

results. Among these ten patients were three with acute gallbladder disease, one with a gastric ulcer that had perforated posteriorly into the pancreas, two who had empyema of the gallbladder and four who had alcoholic gastritis. (Table II.)

cedures, must be performed early in the course of the disease or the determination is of little value. (Table III.)

The antithrombin titer can be performed daily and our data reveal that a fall in antithrombin level correlates extremely well with

Table III
A COMPARISON OF THE PLASMA ANTITHROMBIN, SERUM AMYLASE AND SERUM LIPASE TESTS

Factors Compared	Plasma Antithrombin	Serum Amylase	Serum Lipase
1. Time required to per-			
form tests	10 to 25 min.	2 hr.	24 hr.
2. Period of illness during	TT1 1	T: . 0 . 041	16 6 . 241
which test is diagnostic	Throughout the acute phase of the illness	First 8 to 24 hr.; rarely be- yond this point	After first 24 hr.
3. Period of illness during which test can be per-			
formed	Plasma can be refrigerated and reliable results obtained	Must be performed immediately	No result until 24 hr. after beginning test
4. Chemical agents	Simple, stable	Complex, unstable	Complex, stable
	Highly specific for acute pan- creatitis	Positive in intestinal obstruc- tions, renal disturbances, uremia, peritonitis, paroti- tis	Highly specific for acute pan- creatitis

It is at once apparent that in those instances in which the pancreas is secondarily involved as the result of direct extension, as by posterior perforation of a gastric ulcer or through the duct of Wirsung from a diseased gallbladder, positive antithrombin determinations may be obtained. In the remaining 294 patients (97.3 per cent) of the group with the "acute surgical abdomen" the antithrombin titer was not elevated. We consider this negative correlation in cases unassociated with pancreatic disease of considerable clinical significance. It indicates a high degree of specificity of the antithrombin titer as an aid in the differential diagnosis of acute surgical abdominal diseases.

One of the chief advantages of the antithrombin titer over the serum amylase or lipase determinations is the relative ease and rapidity with which the test can be performed. In typical instances, at the end of a ten-minute period of incubation, the antithrombin titer is sufficiently high to support a diagnosis of acute pancreatitis. Another distinct advantage of the antithrombin test is the elevated titers that are obtainable throughout the acute phase of the illness. Serum amylase determinations, in addition to being highly complicated laboratory proclinical improvement. On the other hand, maintenance or occasional rise of daily anti-thrombin levels suggests extension of the acute inflammatory process. In other words, persons with acute pancreatic edema or interstitial pancreatitis prior to development of the necrotic phase of hemorrhagic or suppurative pancreatitis often show persistently high anti-thrombin levels together with daily fluctuation and increase in titer. Therefore, the anti-thrombin titer is also of value in determining prognosis.

In estimating the antithrombin titer it is technically of advantage that the oxalated or citrated blood samples can be refrigerated for twenty-four to forty-eight hours without appreciable deterioration or significant interference with the reliability of the test.

#### SUMMARY

The antithrombin titer for acute pancreatitis was markedly elevated in fifty of fifty-five proven cases of acute pancreatitis. In 97 per cent of a control series of 304 patients with acute surgical abdominal diseases the antithrombin titer was normal. The ten patients

with elevated titers (3 per cent) included three with acute gallbladder disease, four with acute alcoholic gastritis, two with empyema of the gallbladder and one with a perforated peptic ulcer. In each of these ten patients it is presumed there was secondary acute pancreatitis. In none of 150 normal controls was the antithrombin level elevated.

#### CASE REPORTS

Case I. B. T., a forty-eight year old house-wife, was admitted to the hospital because of the sudden onset of severe, knife-like, epigastric and left upper quadrant pain. Pertinent findings on physical examination included abdominal distention, and spasticity and moderate rigidity of entire upper abdomen. Laboratory data were as follows: white blood count 22,000 polymorphonuclears 92 per cent, lymphocytes 8 per cent, sedimentation rate very rapid. The urine revealed 2 plus glucose, 1 plus acetone and serum amylase 560 units (Somogyi). The clinical impression was acute pancreatitis.

An antithrombin titer was performed and the results were as follows:

Incubation	Clotting Time (sec.)		
Interval (min.)	Normal Control	Patient B. T.	
1	17	37	
5	29	73	
10	61	282	
15	120	>5 min.	
20	182	>5 min.	

Case II. L. A., a forty-eight year old white housewife, was admitted to the hospital complaining of upper abdominal pain of several hours' duration. The pain which radiated to the upper thoracic vertebral region was accompanied with nausea and vomiting of marked degree. Physical examination revealed tenderness and rebound tenderness in both upper quadrants. Essential laboratory data were white count 18,500, polymorphonuclears 88 per cent and serum amylase fluctuations between 250 Somogyi units on the evening of admission to a level of 730 units on the second day of her hospital stay. The diagnosis was acute pancreatitis.

An antithrombin titer was performed on the fourth day of her hospital stay and the diagnosis of acute pancreatitis was confirmed.

Incubation	Clotting Time (sec.)		
Interval (min.)	Normal Control	Patient L. A	
1	15	34	
5	26	76	
10	58	5 min.	
15	110	5 min.	
20	170	5 min.	

Case III. N. K., a fifty-four year old white housewife, entered the hospital in a shock-like state. A history was obtained of the sudden onset of nausea, vomiting and agonizing, epigastric pain six hours prior to admission to the hospital. Pertinent physical findings included board-like rigidity of the entire abdomen in a patient who was deeply cyanotic and in shock. Laboratory data were as follows: hematocrit 64 per cent, white blood count 25,000 and polymorphonuclears 93 per cent. Urine showed 3 plus glucose, 1 plus acetone, Sulkowitch positive and serum amylase 1,600 Somogyi units.

Despite the institution of measures to combat shock, dehydration and obvious infection, the patient expired twelve hours after admission to the hospital. An autopsy was performed and acute suppurative pancreatitis was found.

An antithrombin titer was performed six hours following admission to the hospital.

Incubation Interval	Clotting Time (sec.)		
(min.)	Normal Control	Patient N. K	
1	16	33	
5	28	79	
10	54	5 min.	
15	116	5 min.	
20	177	5 min.	

Case IV. This case is presented in order to illustrate the group in which the antithrombin titer correlates extremely well with the clinical course of the disease process.

J. M., a forty-four year old colored dressmaker, was admitted to the hospital ten days prior to the performance of the antithrombin test. On admission she presented findings suggesting the presence of an acute abdomen and

an exploratory laparotomy was performed. An acute pancreatitis was discovered at operation. Her postoperative course was entirely uneventful. At the time of performing our test the patient had been well and was ambulatory for five days. We considered this test negative. The diagnosis was subsided acute pancreatitis.

Incubation Interval	Clotting Time (sec.)		
(min.)	Normal Control	Patient J. M.	
1	17	16	
5	25	23	
10	56	54	
15	110	114	
20	184	176	

CASE v. E. B., a forty-six year old colored male, entered the hospital complaining of nausea and vomiting of one day's duration associated with epigastric pain. On physical examination his abdomen presented rigidity and exquisite tenderness in the right upper quadrant and epigastrium. A flat film of the abdomen revealed elevation of the right dome of the diaphragm. Laboratory data revealed albumin 2.9, globulin 3.0, A/G ratio 0.97, total protein 5.9, CO2 combining power 56, amylase on the day of admission 537 Somogyi units, on the following day amylase 632 units. An antithrombin titer was performed on the fourth day of his hospital stay. The final diagnosis was acute pancreatitis.

Incubation Interval	Clotting Time (sec.)		
(min.)	Normal Control	Patient E. B.	
_ 1	15	31	
5	27	64	
10	58	312	
15	114	>5 min.	
20	172	>5 min.	

Case vi. J. Y., a thirty-six year old colored male, entered the hospital three weeks previously because of generalized abdominal pain accompanying nausea and vomiting. On the

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basis of marked tenderness over McBurney's point a laparotomy was performed. A gangrenous appendix was removed. His postoperative course was uneventful and he was discharged on the eighteenth day. He was readmitted to the hospital one week later because of the recurrence of abdominal pain accompanied with marked abdominal distention. A fluid wave was readily demonstrable upon examining the abdomen. He was intubated (Miller-Abbott) with immediate relief. Blood amylase during this admission varied from 520 to 714 (Somogyi). The diagnosis was acute pancreatitis. An antithrombin titer was performed on the sixth day of his second admission.

Incubation Interval	Clotting Time (sec.)		
(min.)	Normal Control	Patient J. Y.	
1	17	37	
5	29	64	
10	59	290	
15	119	>5 min.	
20	181	>5 min.	

Case VII. A sixty-four year old colored man, an alcoholic with diabetes, has been in the hospital repeatedly from 1946 to 1949. A diagnosis of empyema of the gallbladder was made in 1948 but no evidence of pancreatic involvement was noted on surgical intervention at that time. The patient had repeated episodes of midepigastric pain with vomiting on several occasions since 1948. At the time of his present hospital admission the chief complaint was upper abdominal pain radiating to the left costal margin. The pain was not relieved by alkalies.

Physical examination revealed there was marked tenderness of the epigastrium and right hypochondrium with rebound tenderness in the right upper quadrant. Arteriosclerotic heart disease and prostatic hypertrophy were noted. Laboratory data were as follows: serum amylase 372 mg. per 100 cc; sugar tolerance test showed a blood sugar level of 160 mg. per cent on fasting; 220 mg. per cent for one-half hour, 293 mg. per cent for one hour and 266 mg. per cent for two hours. Urine specimens showed 2 plus glucose. An antithrombin titer was determined. The results were as follows:

Incubation Interval	Clotting Time (sec.)		
(min.)	Normal Control	Patient	
1	16	27	
5	29	75	
10	58	5 min.	
15	110	5 min.	
20	160	5 min.	

The clinical diagnosis was acute pancreatitis, confirmed by the high antithrombin titer.

CASE VIII. A forty-seven year old colored man was admitted to the hospital because of morning epigastric pain, associated with cyanosis and collapse of several hours' duration. In the past the patient experienced upper abdominal pain for the past three years, occurring one hour after eating. Relief was obtained by ingestion of food and taking alkalies. The patient stated he had lost weight. Physical examination revealed tenderness and rebound tenderness over upper abdomen. Laboratory studies revealed: serum amylase 112. Sugar tolerance test showed 68 mg. per cent sugar on fasting, 119 mg per cent for one-half hour, 170 mg per cent for one hour; 110 mg. per cent for two hours and 150 mg. per cent for three hours. Urine specimens gave negative reactions for sugar. Icteric index was 2. Thymol turbidity was 4.6 units. Prothrombin time was normal. Serum albumin measured 4.5 gm., globulin 3.7 gm. and cephalin flocculation was negative.

An antithrombin titer was performed. The results were as follows:

Incubation Interval	Clotting Time (sec.)		
(min.)	Normal Control	Patient	
1	15	29	
5	30	72	
10	56	5 min.	
15	110	5 min.	
20	180	5 min.	

The diagnosis was acute pancreatitis.

CASE IX. A diabetic, alcoholic, forty-two year old white man, entered the hospital complaining of anorexia, vomiting and abdominal pain. The pain persisted as a deep ache in the epigastrium radiating through to the back. There were previous occasions when ingestion of alkalies and food, especially milk, would bring relief. At the present time the pain is constant and aggravated by the drinking of alcohol. The patient stated that during the past several years he had had five to ten fatty stools daily. In the past year there has been a loss of weight,

approximately fifteen pounds.

Physical examination revealed he is a well developed, well nourished man with moderate epigastric tenderness. No abnormalities were noted. Laboratory data revealed serum amylase was 205 mg. per cent. The serum amylase dropped to 63 after four days. Hemogram was normal, sedimentation rate 63 mm., feces were peanut butter in appearance. Liver function tests were normal as were tests of gastric analysis. Sugar tolerance test was 105 mg. per cent on fasting, 220 mg. per cent for one-half hour, 243 mg. per cent for one hour, 190 mg. per cent for two hours and 103 mg. per cent for three hours. Urine specimens varied from 1 to 4 plus reactions. An antithrombin titer was determined. The results were as follows:

Incubation Interval	Clotting Time (sec.)		
(min.)	Normal Control	Patient	
1	17	27	
5	27	75	
10	57	5 min.	
15	120	5 min.	
20	180	5 min.	

The clinical diagnosis was chronic relapsing pancreatitis in acute exacerbation confirmed by high amylase and high plasma antithrombin activation.

CASE X. W. L., a twenty-six year old colored male, was admitted to the hospital five days after the onset of severe epigastric pain which radiated to the scapular area on both sides, and was associated with persistent nausea, vomiting and anorexia. The patient stated that after bouts of alcoholic excess severe epigastric pain would appear associated with a pattern of nausea, vomiting and anorexia. The patient was afebrile and physical examination at the time of admission showed no abnormalities other than generalized abdominal tenderness without the rigidity. Laboratory data revealed

serum albumin 4.7 gm. per cent, globulin 2.6 gm. per cent, cephalin flocculation one plus, bromsulphalein retention 10 per cent, van den Bergh 0.1 direct, 0.3 indirect, thymol turbidity 6.6, alkaline phosphatase 1.4 units, total cholesterol 216 mg. per cent and cholesterol esters 166.2 mg per cent. Glucose tolerance curve revealed fasting 92 mg. per cent, one-half hour 162 mg. per cent, one hour 164 mg. per cent and two hours 137 mg. per cent. Urine was normal. Serum amylase was 491. Plasma antithrombin titers were markedly elevated. The diagnosis was chronic relapsing pancreatitis in exacerbation.

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## Calcium, Potassium, Magnesium and Amylase Disturbances in Acute Pancreatitis\*

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THE accurate diagnosis of acute pancreatitis and successful management of the resultant therapeutic problem depend upon a sound understanding of the related physiologic changes. In mild attacks of the disease these changes are relatively simple. In severe attacks they may become exceedingly complex and the responsible mechanisms difficult to assess.

The major physiologic reactions although interrelated may be broken down for purposes of discussion and clarity of clinical thought into certain logical groups. In the first group are those specific changes related to the damaged pancreas: absorption and excretion of the pancreatic enzymes;1-4 loss of plasma and, frequently, of blood into the pancreas and adjacent tissue; disturbance of carbohydrate metabolism due to islet damage; transfer of serum calcium into the areas of fat necrosis, producing soap from the hydrolyzed fat; 5-9 inhibitive ileus, probably reflex in nature; and lastly the absorption of fat or hemoglobin, resulting in hyperlipemia,5,10 fat embolism or hemoglobinemia. In the second group are disturbances of the electrolytes. Vomiting, nasogastric suction and the alarm reaction 11 condition the electrolyte pattern. In the last group are the shock phenomena often present in the first few hours of the acute severe cases. Acute renal insufficiency when present further changes the already disturbed electrolyte pattern.

Most of the changes listed in the first group are measurable by laboratory means and form the basis for the diagnosis of acute pancreatitis and, to a lesser extent, the prognosis. The difficulties due to electrolyte disturbance and shock can likewise be followed in the laboratory and are of major importance in treatment.

The high incidence of acute pancreatitis at the Los Angeles County Hospital offers an unusual opportunity for the study of this disease. During the period of this study (April 1, 1945, to April 1, 1950) the average number of new cases per annum was approximately seventyfive. From them we selected for the study of electrolytes twenty-six who were considered to have had a moderate or severe attack of the disease at the onset. One patient from a private hospital was included, making a total of twentyseven. A study of the clinical picture in 452 patients with acute pancreatitis at the Los Angeles County Hospital over a period of sixteen years (1932-1948) has been reported by Paxton and Payne. 12

#### METHODS

Sodium and potassium determinations were made with the Perkin and Elmer flame photometer No. 52A except in a few early cases. The 17-ketosteroids were determined by the method of Talbot et al. 13,14 and the lipid-soluble reducing steroids by the method of Heard et al. 15,16 Magnesium and phosphate were determined by the molybdivanadate method, 17,18 calcium by the Tisdall method 19 and the remainder of the tests by the standard laboratory procedures.

#### Enzymes

Amylase. The absorption of amylase from the pancreatic area results almost invariably in a rise in the serum in the first twenty-four hours of the disease. The urinary diastase values closely parallel those of the serum amylase but return to normal somewhat later. The length of time required depends on the severity of the disease and the rate of healing. In the majority of cases three to ten days suffice. Recurrences,

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complications and chronicity of the pancreatic lesion may alter the pattern and delay the return to normal by days or weeks. But even with repeated attacks the over-all tendency is for healing to occur and the escape of enzymes into the tissues to cease. Because the serum amylase may have returned to normal by the time the patient enters the hospital, both amylase and urinary diastase determinations should be performed. Once the diagnosis is established the course of the disease can be observed by following the concentrations of either. The mechanism of secretion of amylase by the kidney is not known. Presumably amylase passes into the glomerular filtrate but tubular excretion may be possible. We have done twenty-four-hour quantitative studies on the urine in a few patients. These indicate that if amylase comes through freely in the glomerular filtrate most of it is reabsorbed by the tubular epithelium.

The range of serum amylase in the twentyseven patients studied was 350 to 8,571 units.\* Twenty-two entered the hospital in the first twenty-four hours of their illness with an average amylase of 2,540 units. In every instance in which the urinary diastase was estimated on the first day it was as diagnostic as the serum amylase. The return to normal was proven in 10; it occurred between the fourth and twelfth days, the average being 6.3 days. The elevation of the serum amylase is not necessarily correlated with the severity of the disease or prognosis. The explanation for this is evident from the study of autopsy material. The degree of pancreatic damage varies widely. At one extreme is the almost completely necrotic, hemorrhagic gland, often with massive thrombosis of the pancreatic and splenic veins, which would be incapable of producing an elevated blood amylase. At the other extreme is the gland with only moderate necrosis of the acini and little hemorrhage, in which the ducts may contain clear secretion. We have observed glands in this latter condition which had continued to form enzymes, sustaining a high serum amylase until death. The patient with severe hemorrhagic necrosis may be a difficult diagnostic problem if seen after the

serum amylase has returned to normal. It is presumed that it would take at least twenty-four hours for the gland to destroy itself completely; but after this has taken place, the elevated serum amylase may return to normal or low levels. This possibility must be considered by the

Table 1
COMPARISON OF SERUM AMYLASE TITER
IN 330 PATIENTS WITH ABDOMINAL DISEASE

	Units			
Disease	150 to 250	250 to 500	500 to 1,000	Over 1,000
Acute pancreatitis	45	66	45	103
Perforated gastric ulcer	9	6	1	1
Perforated duodenal ulcer	14	8	1	2
Intestinal obstruction	14	5	0	0

physician in evaluating amylase tests made more than twenty-four hours after onset. Fortunately it is in this group that hypocalcemia is of value in diagnosis.

A wide variety of diseases give rise to an increase in the serum amylase. Because of the importance of the amylase in differential diagnosis of those diseases giving rise to abdominal symptoms, we reviewed the clinical diagnosis on all patients (exclusive of those with mumps) having a high amylase reported from the chemistry laboratory between April 27, 1944, and April 27, 1948. A breakdown of the results is given in Table 1. From this table it is evident that levels above 500 units of serum amylase were due in the great majority of patients to acute pancreatitis. Perforation of the intestinal tract into the peritoneal cavity, most commonly due to ulcers of the stomach or duodenum, rarely produced a serum amylase of over 500. The majority were under 250. In those instances of intestinal obstruction with elevated serum amylase the level was usually under 300. In a total of nineteen cases of intestinal obstruction only one had a serum amylase above 300. Among the miscellaneous conditions which may give rise to abdominal symptoms are uremia with nausea and vomiting, dissecting aneurysm and non-specific gastroenteritis. One patient in uremia who had severe abdominal pain, nausea, vomiting, high amylase and a low serum calcium (due to renal insufficiency) with tetany at the

<sup>\*</sup>The test for amylase activity in our laboratory is done by a modification of Somogyi's<sup>2,3</sup> method. It is measured by the hydrolysis of a starch solution under given conditions and one unit is equivalent to 1 mg. of sugar per 100 cc. of the fluid in question. The normal in our laboratory is considered to be below 150 units in the serum and below 1,000 units in the urine.

time of entry to the hospital was a particularly confusing clinical problem. It is of interest that the highest sustained serum amylase we have seen, averaging 4,000 to 16,000 day after day, was in a patient with bronchogenic carcinoma and liver metastases. The pancreas was normal at autopsy.

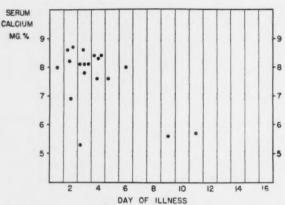


Fig. 1. Lowest serum calcium by day of illness in nineteen patients with acute pancreatitis.

The examination for amylase of peritoneal fluid obtained at surgery or by diagnostic abdominal tap is important. This test when made in an individual with pancreatitis is frequently diagnostic. The fluid as a rule is light brown to bloody due to hemorrhage and hemolysis around the pancreas. Small fat droplets secondary to fat necrosis float on the surface. The titer of amylase is high, usually above that in the serum. In our experience normal peritoneal fluid collected at surgery does not contain over 100 units of amylase.

Lipase. The older methods for lipase are both tedious and of doubtful accuracy, at least in our experience. It seems probable that studies using the newer methods<sup>20</sup> will make it possible to evaluate more properly the importance of serum lipase in acute pancreatic necrosis.

#### Serum Electrolytes

Calcium. The serum calcium was below 9 mg. per cent in nineteen of the twenty-seven patients at some time between the first and ninth day of the disease. The lowest calcium recorded was on the second to fourth day of the disease in fourteen of the nineteen. (Fig. 1.) In one instance the only serum calcium determined was 5.6 mg. per cent on the day of death, nine days after onset. The return of the serum calcium to normal was demonstrated in six. This occurred by the fourth to sixteenth day; the average was

9.3 days. However, this can well vary from one group to another. The degree of the hypocalcemia bears some relation to the severity of the disease and probably should be looked upon as a quantitative equivalent of the amount of fat necrosis. Twelve of the nineteen patients had a serum calcium of 8 to 8.6 mg. per cent. Three were between 7 and 7.9 mg. per cent and four were under 7 mg. per cent. Previously<sup>6</sup> we indicated that moderately severe attacks of pancreatitis were associated with a serum calcium of 8 to 9 mg., severe necrosis with levels of 7 to 7.9 and fatal termination with levels below 7. The results now indicate that while this is essentially correct, levels below 7 may occur in patients who recover, as did two in this group. Both were extremely ill. One (E. O.), who was pregnant,\* had only one reading below 7 (6.9 mg. per cent). As the serum calcium in pregnancy is often slightly lowered, this low figure may not have quite the same significance it would in the non-pregnant individual. The second patient (W. I.), with a serum calcium of 5.3, recovered only after a stormy course characterized by shock, convulsions and lower nephron nephrosis. This patient received 4,700 mg. of calcium intravenously as calcium chloride over a period of five days. Meanwhile the serum calcium rose only from 5.9 to 8.8 The failure of the serum calcium to rise further is difficult to explain. This patient received over twice the maximum amount of calcium (1,600 mg.) we have ever recovered from the areas of fat necrosis at necropsy.

Of the five fatalities in this group autopsies were obtained in three. Two had severe hypocalcemia and extensive fat necrosis. The third had a serum calcium of 8.1 the day of death. Necropsy revealed minimal fat necrosis, extreme hemorrhage around the pancreas and extensive hemorrhage into the wall and lumen of the intestine. No necropsy has revealed minimal fat necrosis associated with severe hypocalcemia.

It must be recognized that there may be mechanisms involved in the fall of the serum calcium<sup>9</sup> other than its use in the formation of soaps. The excretion of calcium into the bowel may occur in excessive stimulation of the adrenals by ACTH.<sup>22</sup> As these patients are on nasogastric suction, bowel movements as a rule do not occur until suction is removed and the patient begins to take food. We have not checked

\* This patient's case history has been reported in detail in another paper.\*1

the stools following suction for possibly increased calcium content.

It is of interest that it takes from four to sixteen days for the serum calcium to return to normal. This indicates that the compensatory mobilization of calcium from bone, possibly by parathyroid hormone, occurs slowly. Little is known of the mechanism by which serum calcium is increased under these circumstances. The serum calcium level was of value in the diagnosis of severely ill patients who on entry to the hospital had a normal amylase. The following patient illustrates this, also that a low calcium associated with little elevation of the amylase implies mechanisms of the gravest magnitude:

R. M., a thirty-two year old Mexican male, entered the hospital on September 23, 1945, because of epigastric pain and vomiting of six days' duration. This had followed a twentyfour-hour alcoholic debauch. The temperature was 98.2°F., pulse 144 and blood pressure 190/ 145. There were severe epigastric tenderness, abdominal distention and hypoactive peristalsis. Severe ileus was disclosed by x-ray. Serum amylase was 120 units on September 25th. In order to differentiate pancreatitis from intestinal obstruction two additional laboratory tests were done. Serum calcium was 5.6 mg. per cent. The serum was grossly milky in color. The hemorrhagic fluid obtained on abdominal tap contained 600 units of amylase per 100 cc. On this date the blood pressure began to fall, pulse became weak and bilateral hemorrhagic discoloration was noted in both flanks (positive Turner sign). With these findings a diagnosis of severe hemorrhagic pancreatic necrosis was made. The patient died September 26th and the diagnosis was confirmed at autopsy. There was widespread thrombosis of the pancreatic and splenic veins. The portal vein was partially thrombosed and extensive fat necrosis was present.

The lag in return of the serum calcium to normal is also of diagnostic importance in another group of patients with acute pancreatitis—those who are improving and come into the hospital after the blood amylase and urinary diastase have returned to normal. If sufficient fat necrosis is present, the serum calcium will be below normal—an aid in substantiating a clinical diagnosis of subsiding acute pancreatitis.

In thirteen cases the serum phosphorus was determined and it was found to be normal in seven and decreased in six. The decreased phosphorus levels were associated with considerable degrees of hypocalcemia in all but one instance and with some degree of hypokalemia in all six.

Because of the relation of serum calcium to the blood proteins, serum albumin and globulin determinations were made in fourteen patients. The serum albumin was under 4 gm. per 100 cc. in seven. No definite correlation with the low serum calcium could be determined in this group as compared with those with serum albumin above 4.

Potassium. The results in the potassium studies disclose that nineteen of the twenty-seven patients developed hypokalemia. (Fig. 2.) Three had normal levels and recovered. Five had normal or elevated levels associated with a fatal ending. One of these patients (R. B.) received potassium therapy beginning on the eighth day of illness. In six individuals only a single reading was obtained; in the remainder two to eighteen were made in each instance. Because it was noted that a serum deficit might occur on the first or second day of the disease, twenty-four-hour urine samples were obtained for total potassium excretion in a few patients and a complete potassium balance study was carried out in one patient.

The severity of the hypokalemia was variable. In three the serum potassium was 6.8 to 9.6, in ten it was 10 to 12.8, and in six it was 14 to 14.7 mg. per cent. No symptoms attributable to hypokalemia were described in the histories; however, characteristic symptoms of hypokalemia are masked in severe pancreatitis. The return of serum potassium to normal usually occurred four to six days after oral feeding was started.

In an attempt to arrive at the cause or causes of such a hypokalemia its relationship to the day of the disease, to alkalosis, intravenous administration of saline solution, nasogastric suction and finally to adrenal function was considered. Hypokalemia occurred in two patients on the first day of their disease. One (W. W.) had been on suction and had received 1,000 cc. normal salt solution and 1,000 cc. 5 per cent glucose within twelve hours before a serum potassium of 12.1 and sodium of 286 mg. per cent were determined. In the second (S. J.) no saline had been given and nasogastric suction had been going for two and a half hours, yet the serum potassium was 14.6 mg. per cent. On the second day of their disease three patients on suction and intravenous fluids had levels of 12 to 12.2 mg. per cent. A further fall in serum potassium usually occurred in patients kept on this regimen; the lowest figure reached was 6.8 mg. per cent (1.74 mEq.) after fourteen days. The latter results are not unexpected in view of the facts now known concerning the absence of potassium intake<sup>23</sup> but the low serum potassium on the first day of the disease noted in two patients

end of the second day, at which time the serum potassium was 13.8.

On a recent patient (R. B.) a balance study accompanied with determination of urinary steroids was done in order to examine further the mechanism of the increased potassium out-

DAYS	1	2	3	4	5	6	7	8	9	10	11	12	13	. 14	15	16
LH		14.5		24.5		10.8										
18.									142			12.5		6.8		9.5
LN		12	10	10	10		12.5	13	13		13			13		16.
WN.			.29	14.1												
EL.												12.6				12.
N.J.	-		9.2				12									
C.S.		15.2				142										
CC.					14.2	15.5										
D.E.		14		14		14.5			17.2		17.2					
H.S.				10.9			11.4									
C.M.				14.9			14.7									
R.B.		12	141	13	13,2	12.2	11.1	122	13.3	13.8				21		
S.J.	14.6		13.8		12			U.6		116		13.3			15.6	
A.D.			16	14	16			16	15							
E.Q.	-	13.1	11.1			11.3		10.7	11.3						16	
N.P.		12.2														
ww	12.1													ATES		
AT.				14.2										SUCTION K		/.

Fig. 2. Low serum potassium in eighteen patients with acute pancreatitis by day of illness and showing relationship to gastric suction; (record of nineteenth patient, W. I., not included).

can hardly be explained by intravenous saline administration or nasogastric suction.

In none of the twenty-seven patients was alkalosis diagnosed. In alkalosis generally the serum potassium is low. The carbon dioxide combining power was determined in nine patients; the range was normal in all but three, these being 20, 36, and 40 volumes per cent, respectively. In view of the characteristic severe vomiting of acute pancreatitis it is noteworthy that alkalosis is so infrequent.

Our observations on twenty-four-hour output of potassium and sodium in the urine are too scanty to be conclusive, but a sizable amount of potassium in the urine without any intake was observed three times. One patient (R. H.) had 1.32 gm. in the urine on the third day of his disease. C. C. had 3.4 gm. on the fourth day and O. E. had a total of 4.94 gm. for the second, third and fourth days. A total two-day loss of 3.34 gm. potassium was noted in S. J. whose only intravenous fluid therapy had consisted of 1,000 cc. normal saline intravenously by the

put. The severity of this patient's illness was attested by a serum calcium of 7.3, semi-coma, fall in blood pressure and all the abdominal findings of pancreatitis. Her condition was critical on the eighth day of illness when potassium therapy was begun. Also on this day there was an eosinopenia of nineteen cells per cubic millimeter (normal, 150 to 250). Twenty milligrams of ACTH produced a 32 per cent drop. On the twenty-fourth day of the disease when the patient was ambulatory the eosinophil count was 1,144 and 20 mg. of ACTH produced a 47 per cent fall. The important laboratory results are concerned with the relation of the potassium and nitrogen balances to urinary steroids. (Fig. 3.)

The movement of potassium in this patient can be accounted for by the breakdown of body protoplasm and loss of the liberated potassium in the urine. The loss of 5 to 14 gm. of nitrogen daily is greater than would be expected from starvation alone. This was accompanied with a potassium loss of 0.5 to 1.32 gm. This ratio of

nitrogen to potassium of 10: 1<sup>24,25</sup> is that expected in breakdown of body protoplasm. Such a loss might be explained by breakdown of tissue in and around the pancreas and/or the excessive secretion of 11-oxysteroids. The output of 7 mg.

quantitated nor was non-protein nitrogen determined in the group routinely, so the exact role of renal failure cannot be stated. A rise in serum potassium is commonly noted in acute types of renal failure.<sup>27</sup>

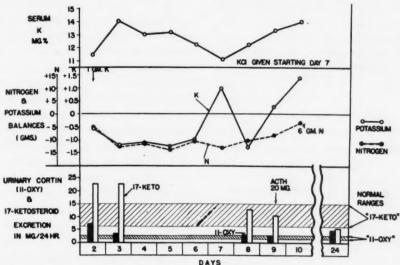


Fig. 3. Patient R. B., study of potassium, nitrogen and steroids in a case of acute pancreatitis by day of disease.

of neutral lipoid-soluble reducing substances in the urine in eleven hours compared to a normal twenty-four-hour output of 1 to 2.5 mg. appears particularly significant. The negative nitrogen and potassium balances in patients receiving ACTH and cortisone therapy noted by Sprague<sup>26</sup> would lend credence to this explanation. The high titer of 17-ketosteroids (26 mg. in eleven hours on the second day) indicates that increased secretion of anabolic hormones could counteract to some extent the action of the 11-oxysteroid group. It may be that this pattern of potassium change is non-specific, one that occurs in more than one disease in which there is extreme tissue damage.

Hyperpotassemia. In contrast to the deficits in the patients who recovered, normal or high levels of potassium were noted in all who died. (Table II.) Two factors are most likely responsible, namely, the great amount of tissue breakdown with the associated hemolysis of erythrocytes in hemorrhagic pancreatitis and, secondly, renal failure due to shock, hemoglobinemia or other mechanisms. In two cases the first factor was evident by the brown color of the serum although the pigment was not identified by spectrographic examination. The factor of shock and renal failure probably operates to some degree in all fatalities. Urine output was not

Magnesium. Because the etiology of tetany in pancreatitis was not always attributable to hypocalcemia, 6 we suspected that a low serum magnesium might result from the use of this ion in the formation of soaps about the pancreas. In two autopsies 40 and 65 mg. of magnesium over

Table II SERUM POTASSIUM, MG. PER CENT, IN FATAL PANCREATITIS BY DAY OF ILLNESS

Days	R. M.	O. R.	Z.	K. C.	С. Н.
1 2 3		31.3 Exitus	26 Exitus	19	
4 9 10 11	23.6 Exitus			Exitus	18.7 26.6
12					41.4 Exitus

and above that found in controls were recovered from the areas of fat necrosis. Whether the loss of such amounts would lower serum magnesium is questionable because of the large intracellular reserve of this ion. Serum magnesium determinations were done on twenty patients in this series. Hypomagnesemia (normal in our laboratory is 1.8 to 2.2<sup>17</sup>) was demonstrated in four. (Table III.) From these studies and other unpublished data it would appear that when hypomagnesemia does occur in the first four or five days of the disease it is of short duration—twenty-four to

TABLE III
LOW SERUM MAGNESIUM (MG. PER CENT) BY DAY
OF DISEASE IN FOUR PATIENTS WITH ACUTE
PANCREATITIS

Days	R. H.	S. J.	K. C.	С. Н.
1		1.5		4.5
2	1.3	1.9	0.95	1.5
4 5 6	1.5	1.2	Death	Death
	1.9		2000	
7		1.8		

forty-eight hours. It seemed to bear no relationship to the fall in serum calcium or potassium.

Acid-base Balance. The only changes in acid-base balance were in the three patients with a carbon dioxide combining power below normal. None was above. The blood chlorides were normal in most instances and their level could not be correlated with serum sodium or any of the other ions discussed.

Sodium. Serum sodium determinations were made in twenty-two of these cases. In eight levels of 295 mg. per cent or less were obtained. These were all encountered during the first nine days of illness; six of the eight were found in the first three days. The lowest was 276, seen in R. M. on the ninth day of his illness and before gastric suction was begun. There had been intermittent vomiting for one week but none for two days before the serum level was done. During these two days he had been eating a bland diet. In R. B., on whom a balance study was being made, the serum level upon entry and for the first three days was between 312 and 316 mg. per cent. The level then slowly fell until it reached 295 on the sixth day. During these six days nasogastric suction was in place and the patient was kept in a positive sodium balance by 5 gm. sodium per day. On the seventh day the level rose to 315 and for the first time the patient was in negative sodium balance.

No good correlation could be obtained between the serum sodium levels and any of the following: amount of vomiting, severity of disease, or plasma levels of chloride, potassium, non-protein nitrogen and carbon dioxide combining power.

### ELECTROCARDIOGRAPHIC CHANGES

The electrocardiogram is a useful procedure for the study of electrolyte variations caused by acute pancreatitis as well as other conditions. 28 Changes in length of the Q-T interval are usually associated with alterations in the serum calcium levels. Potassium, on the other hand, affects the height of T waves and at times the conduction system. Such abnormalities were seen in thirteen of the seventeen patients in this group who had electrocardiograms. However, in other diseases exceptions to this have been found. 28

Occasionally disturbances in cardiac rhythm may occur.<sup>29,30</sup> In rare instances electrocardiographic changes of pericarditis are seen. These are produced by the extension of fat necrosis into the thoracic cavity and onto the visceral pericardium. The entire problem will be more fully discussed elsewhere.<sup>30</sup>

### HYPERLIPEMIA, FAT EMBOLISM AND HEMOGLOBINEMIA

Hyperlipemia manifested by a grossly milky serum may accompany acute pancreatitis. In some instances this occurs along with a high blood sugar and subsides under insulin therapy and healing of the disease. <sup>10</sup> In other patients hyperlipemia occurs without evidence of diabetes. In a previous study <sup>5</sup> we noted that the serum lipids might rise and that widespread fatal fat embolism could occur. This was due to entrance of the products of fat injury into branches of the portal veins. In the present series two patients had a grossly milky serum. One died (R. M., see case report); the other recovered.

In two patients (C. H. and J. Z.) the serum before death contained a brown pigment considered to be hemoglobin. This was apparently due to absorption of hemoglobin or some breakdown product from the areas of hemorrhage in and around the pancreas. At necropsy the kidneys of C. H. contained many pigmented casts and other evidence of lower nephron nephrosis. This explained the clinical picture as the patient was treated for anuria before a history of the abdominal symptoms was elicited and a serum amylase test was done. To our knowledge this clinical and pathologic syndrome of lower

nephron nephrosis due to hemoglobinemia in pancreatic necrosis has never been described in the literature.

#### COMMENTS

Acute pancreatic necrosis is unique in regard to the wide variety of physiologic changes that result. Few diseases show such diversity.

The simplicity and importance of the amylase test have been justifiably emphasized. 1-4 For diagnostic purposes the day of illness is of utmost importance in interpretation of the concentrations of the serum amylase and urinary diastase. Other acute diseases of the abdomen giving an elevated serum amylase, usually under 500 units, must always be considered in differential diagnosis.

The serum calcium may be a diagnostic aid in cases of extreme destruction of the gland or in those who enter the hospital after the serum amylase and urinary diastase have returned to normal. Its value in prognosis<sup>8,9</sup> and treatment should be further investigated.

Only one report of hypokalemia was noted in the literature. Investigation of the metabolism of potassium and nitrogen and the role of adrenal steroids in acute pancreatitis has only begun. Their importance in diagnosis or treatment may be overshadowed by their status as a physiologic component of the alarm reaction. The pronounced lymphopenia uniformly noted by Herford in acute pancreatic necrosis and the eosinopenia in R. B. on the eighth day of illness are further evidences of excessive adrenal activity of the 11-oxysteroids.

The magnesium and sodium levels are affected less frequently. The serum magnesium may or may not be of importance. It should be determined in patients with tetany. The low sodium values were unexpected and are as yet the most difficult of all to understand.

The electrocardiographic changes due to altered serum calcium or potassium levels in pancreatitis may be misdiagnosed as indicative of coronary disease and the patient so treated, as we have observed at least twice.

The therapeutic implications of the electrolyte changes are obvious. The use of proper therapeutic amounts of saline, potassium and calcium as an adjunct to more specific treatment is now a clinical responsibility. The marked nitrogen loss in the urine would indicate a need for vigorous protein replacement.

Hyperlipemia and hemoglobinemia occasion-

ally occur, and their presence is easily suspected by gross inspection of the serum.

### SUMMARY AND CONCLUSIONS

1. Twenty-seven patients with moderate to severe attacks of acute pancreatitis were studied for serum calcium and potassium changes. Serum magnesium, sodium, chloride and phosphate determinations were made in some instances. An electrolyte balance study and estimation of urinary steroids were made in one patient.

2. Hypocalcemia occurred in nineteen (70.1 per cent) of the twenty-seven cases, most often on the second to fifth day of illness. Levels below 7 mg. per cent were noted four times; two of the patients died and two recovered.

3. The serum calcium is of diagnostic help in those patients with complete destruction of the pancreas or those who are seen late in the disease—situations in which the serum amylase and urinary diastase may be normal.

4. Hypokalemia occurred in nineteen (70.1 per cent). Levels below 12 mg. per cent were noted eight times. Urinary loss, intravenous glucose, nasogastric suction, absence of potassium intake and increased 11-oxysteroids secretion all have to be considered in the etiology.

5. An extremely high output of neutral lipidsoluble steroids in the urine, 7 mg. in eleven hours, was observed in one patient.

6. Low serum magnesium levels were noted four times; these were of short duration.

7. Hyponatremia was seen in six of twenty-seven patients. The reasons for this are not clear.

8. Electrocardiograms typical of low potassium and calcium were observed in thirteen of seventeen cases.

9. Hyperlipemia in two cases and hemoglobinemia in two instances emphasize the relative occurrence of these interesting phenomena.

10. The serum amylase was studied in a larger group of patients with diverse diseases. Elevated levels, but not exceeding 500 units, are not infrequent in other acute abdominal diseases such as perforation of the bowel and intestinal obstruction. Dissecting aneurysms and uremia are occasionally confusing.

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## Charcot Joints and Infectious-vascular Lesions of Bones in Diabetes Mellitus\*

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The problem of diabetic neuropathy and its manifestations has intrigued and baffled physicians for over eighty years. The fundamental nature of this process and the direct relationship of diabetes mellitus to it remain obscure. As intermediate or contributing mechanisms in its pathogenesis arteriosclerosis of the vasa nervorum, toxic effects of glucose and ketone bodies, vitamin B deficiency, autonomic dysfunction, infection, idiopathic myelin catabolism and local carbohydrate deprivation have been suggested. 1-5

Early descriptions of the neuropathic phenomena emphasized sensory disturbances, such as nocturnal muscular cramps, anesthesia, analgesia and loss of vibration and position sense in the affected parts, usually the lower extremities. Diminution and loss of the patellar and Achilles tendon reflexes also were noted. Later, muscular weakness, atrophy and paralysis, trophic ulcers, optic neuritis, loss of pupillary response to light, urinary bladder dysfunction, bowel disturbances such as nocturnal diarrhea and evidences of autonomic imbalance were ascribed to involvement of the appropriate neuro-anatomic structures by the diabetic neuropathologic process.

Another particularly interesting manifestation attributed to diabetic neuropathy is the development of bony lesions of the foot similar to those of the Charcot joint originally described<sup>6–8</sup> as occurring in syphilis of the central nervous system and, shortly thereafter, in syringomyelia.

Charcot joints also have been described in peripheral nerve and spinal cord lesions caused by congenital malformations, trauma, infections, tumors, callus formation, leprosy and lead poisoning. They have been produced experimentally in animals by operative section of dorsal nerve roots followed with mechanical trauma to distal joints. When diabetic neurop-

athy is added to this list of causative factors, it is seen that the following elements in the production of the joint lesions are common to all: impairment of afferent pain and proprioceptor impulses, intact motor power to the extremity, chronicity of the process and repeated minor trauma to the afflicted joint. Loss of the so-called trophic influences of Virchow and the humoral mechanism of Katsuki are not well substantiated in this respect.

In the available medical literature to date only twenty-three cases of Charcot joints in patients with diabetic neuropathy are found. 4,9-16 Seventeen of these are reported from one institution.18,16 Typically, these patients have had poorly controlled diabetes for many years, with gradual development of signs and symptoms of severe neuropathy and little or no concomitant vascular insufficiency or infection. The lesion appears as a swelling of the mid-portion of the foot, with or without pain, and progresses to loss of both arches of the foot and finally to total disintegration of the tarsal bones and their articulations. Four patients with this type of lesion have been studied recently at the Pennsylvania Hospital and the Benjamin Franklin Clinic. The case reports of the first two patients follow.

CASE I. J. C., a white married male pharmacist aged forty-three years, was admitted to the Pennsylvania Hospital with a history of diabetes mellitus of fourteen years' known duration. During that time the diabetes was under irregular control, with frequent glycosuria occurring, but there were no known episodes of ketosis or coma. He took 30 units of protamine zinc insulin and 10 units of regular insulin separately daily before breakfast and 5 to 20 units of regular insulin before lunch and dinner, according to the amount of glycosuria present at those times.

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About two years prior to this admission he experienced swelling of the right foot which at first disappeared on bed rest but later became constant. Four months before admission he first complained of numbness of the feet and of the finger tips. About the same time he noticed edema of the left foot and an ulcer developed on the right great toe, which healed slowly. Shortly before entry to the hospital he first noted an ulceration on the left great toe and also one under the proximal end of the left metatarsal hones.

He gave no family history of diabetes and his past history was non-contributory. There was no history of venereal disease by name, sign or symptom. A review of the systems revealed chronic intermittent nocturnal diarrhea, with fatty stools, and anemia with pallor and dizziness of three years' duration, morning nausea relieved by food for seven months, and left abducens nerve weakness with diplopia of six weeks' standing. The patient's weight had remained in the neighborhood of 132 to 134 pounds (60 to 61 kg.) for the preceding eight months.

The physical examination on entry revealed the systolic blood pressure to be 176 mm. Hg, with a diastolic pressure of 120 mm. The pupils reacted normally to light and accommodation, and arteriovenous nicking of the retinal vessels, arteriolar sclerosis, round hemorrhages and waxy yellow exudates were seen on ophthalmoscopy. There was generalized pallor of the skin and mucous membranes but no evidences of avitaminosis; the liver was not palpable. Examination of the extremities revealed 4 plus pitting edema of the right foot, ankle and lower leg and 1 plus edema of the left foot and ankle. There was a marked increase in the thickness of the bony structures of the left foot and ankle and a deep, dry, granulating ulcer beneath the left metatarsal heads and a moist shallow ulcer on the tip of the left great toe. The toe tips were warm and there were excellent dorsalis pedis and posterior tibial pulses bilaterally. The skin temperature was normal throughout but there was absence of touch, pain, vibration and position sensation in the feet and ankles bilaterally; hypalgesia over the dorsolateral surface of both legs; loss of vibration sense in the tips of all fingers of the right hand and in the fourth and fifth finger tips of the left hand; tenderness over the course of the femoral and peroneal nerves in both lower extremities; absent patellar and

Achilles tendon reflexes bilaterally and a positive Romberg sign.

Repeated urinalyses revealed specific gravities ranging from 1.010 to 1.018, 2 to 4 plus reactions for albumin and occasional granular casts in the sediment. An initial hemogram included 10 gm. per cent of hemoglobin and 2.6 million red cells per cu. mm. with normal white cell and differential counts. The blood urea nitrogen values varied between 26 and 77 mg. per cent with a total protein of 7.1 gm. per cent, serum albumin of 3.5 gm. per cent, uric acid of 4.6 mg. per cent and cholesterol of 340 mg. per cent. Phenolsulfonphthalein excretion tests showed that 5 to 10 per cent of the dye was excreted in twenty minutes with total two-hour excretions of 30 to 35 per cent. Analysis of the stools revealed steatorrhea without creatorrhea. An electrocardiogram was normal except for evidences of a left axis deviation. Analysis of the gastric secretion revealed less than normal amounts of free hydrochloric acid after stimulation with histamine. Serologic tests for syphilis on blood and several spinal fluid specimens were negative. The spinal fluid protein was elevated.

X-ray examinations of the heart, lungs, mediastinum, abdomen and hands were negative. The spine showed a spina bifida occulta of the fifth lumbar vertebra. Roentgen ray films of the right foot (Fig. 1) revealed marked but incomplete destruction of all of the tarsal bones. with numerous circular defects. There was considerable soft tissue swelling and periosteal proliferation along the lateral margins of the fourth and fifth metatarsal bones as well as the articular portions of the distal tibia and fibula. Examination of the left foot revealed only two indistinct radiolucent areas in the cuboid bone and periosteal proliferation along the fifth

metatarsal.

During the patient's course in the hospital his diabetes was controlled by 42 units of protamine zinc insulin and 14 units of regular insulin given separately before breakfast and a 2,800 calorie diet containing 175 gm. of protein, 300 gm. of carbohydrate and 100 gm. of fat in three equal feedings and a bedtime nourishment.

Additional therapeutic measures included transfusions of whole blood, dilute hydrochloric acid by mouth, a total of 9,000,000 units of penicillin during a fifteen-day period, supplementary vitamins, boric acid solution soaks and furacin ointment applied locally to the pedal ulcerations, and two caudal blocks.

During his hospital stay of thirty-four days the diarrhea ceased and the stools became normal; the hemoglobin concentration rose to 12 gm. per cent and the red cell count to 4.0 million per cu. mm. The blood urea nitrogen concentration remained elevated and the albuminuria and cylindruria persisted. His blood pressure remained elevated to near the level on entry most of the time, occasionally falling as low as 120 mm. Hg systolic and 75 mm. diastolic. The edema of the left foot disappeared and that of the right foot diminished but gross thickening of the solid structures persisted. The pedal ulcerations healed slowly and incompletely. There was no change in the neurologic abnormalities or in the appearance of the bones of the feet by x-ray.

The patient was discharged to home management with diagnoses of diabetes mellitus, diabetic retinopathy, the diarrhea of diabetes, diabetic peripheral neuropathy, diabetic tabes (dorsal sclerosis) with neurotrophic ulcerations and bone lesions (Charcot joints) of the feet, and intercapillary glomerulosclerosis (Kimmelstiel-

Wilson's Disease).

CASE II. E. C., a fifty-four year old housewife, was seen at the Benjamin Franklin Clinic of the Pennsylvania Hospital for a diagnostic survey at which time she gave the following history: In 1916 the patient weighed 140 pounds (63.6 kg.). By 1924 she had gained to 180 pounds (81.8 kg.) and in 1930 she weighed 300 pounds (136.4 kg.). During an admission to another institution in 1930 for study of her obesity a diagnosis of diabetes mellitus was established. Since that time the patient had followed a diabetic diet sporadically and had taken insulin intermittently with resultant poor diabetic control. Her weight ranged between 230 and 250 pounds (104.5 and 114.5 kg.).

Three years prior to her clinic visit she first noted pain in both feet with gradual progression to the point of incapacitation. Nine months before entry gradually progressive edema of the right lower extremity developed and, shortly after its onset, an ulceration developed on the dorsum of the right foot which healed slowly. One week before entry she burned the lateral and adjacent plantar surfaces of her left foot with a hot water bottle.

Immediately prior to being seen here she had been taking 25 units of globin insulin and 15 units of regular insulin daily at irregular intervals.



Fig. 1. Case 1. Right foot; note destructive changes in the tarsal bones. The changes in the adjacent portions of the metatarsals, tibia and fibula are not easily seen in this view.

The patient's mother and a paternal uncle had had diabetes mellitus; the family history was otherwise non-contributory. Except for a history of a kidney condition and rheumatism as a child, the past medical history also was non-contributory.

Review of the systems elicited the following significant findings: emotional lability, visual blurring, exertional tachycardia, dyspnea on exertion, intolerance to dietary fat, frequent bouts of diarrhea with loose yellow stools, pruritus vulvi, dysuria, nocturia, urinary frequency, fleeting pains in the extremities and low back discomfort—all of several years' duration.

On physical examination the patient weighed 257½ pounds (117 kg.) and her blood pressure was 140 mm. Hg systolic and 80 mm. diastolic. The pupils reacted normally to light and accommodation. Ophthalmoscopy revealed arteriolar sclerosis, hemorrhages, colloid deposits and dis-



Fig. 2. Case II. Right foot; the areas of cystic dissolution, sclerosis and periosteal proliferation in the bones of the tarsometatarsal area are seen. The changes in the left foot were similar but less marked.

crete yellow exudates. There were no signs in the eyes or tongue of vitamin deficiency. The lungs, heart and abdomen were normal with no perceptible hepatic enlargement. The legs were edematous, the right more so than the left, with purplish discoloration of the skin, recently healed ulcer scars on the dorsum of the right foot and a recent vesicle due to a burn on the lateral aspect of the left foot. The pedal pulses were not felt in either foot but the skin temperature was normal to the toe tips. Neurologic examination revealed absent vibratory and position sensation in both feet and ankles, hypesthesia and hypalgesia over the lower twothirds of both lower extremities and absent patellar and Achilles tendon reflexes bilaterally.

Urinalysis revealed a specific gravity of 1.010, a trace of albumin and many leukocytes in the sediment. Five fractional urine specimens contained sugar but no acetone. The hemoglobin concentration and erythrocyte, leukocyte and differential blood counts were normal. Serologic tests for syphilis were negative. A blood urea nitrogen level was 8 mg. per cent and a fasting venous blood sugar was 236 mg. per cent. Lumbar puncture revealed crystal clear spinal fluid with normal pressure and dynamics, five lymphocytes per cu. mm., a protein concentration of 0.09 gm. per cent, negative complement fixation test for syphilis and a gold sol curve of ten zeros. A basal metabolic rate was minus 17 per cent. An electrocardiogram was normal. X-ray examinations of the chest and abdomen. were negative. A cholecystogram showed markedly impaired gallbladder function with no shadows of stones. Cystoscopy showed only mild injection of the bladder mucosa; a urine specimen taken at that time was sterile on routine culture. A nutritional survey revealed that her recent daily dietary intake had been low in protein and excessively high in total calories. X-ray examination of the feet (Fig. 2) revealed destruction of the tarsal bones of both feet, more marked on the right than the left, with expansion of the bones, areas of cystic dissolution, areas of sclerosis and periosteal proliferation.

Diagnoses of exogenous obesity, diabetes mellitus, diabetic retinopathy, the diarrhea of diabetes and diabetic neuropathy with sensory impairment and bone changes (Charcot joints) were made and appropriate therapeutic suggestions were forwarded to the referring physician.

Recent articles 15,17 in the neurologic and roentgenologic literature suggest that the bony changes in the feet of patients with diabetes may be entirely secondary to an acute or chronic inflammatory process in the adjacent soft tissues, with chronic arterial insufficiency playing a major contributory role. However, the changes in the tarsometatarsal areas, like those of the two patients described before, seem to be definitely related to the pre-existing diabetic neuropathy. Arteriosclerosis, infection and malnutrition apparently operate only indirectly insofar as they may aggravate the neuropathy. (Fig. 3.)

On the other hand, many diabetic patients have a second, somewhat different type of lesion of the phalanges and metatarsals. These changes, unlike those of the tarsal region, are associated

with infection and arterial inadequacy and occur in extremities in which there are few or no signs of neurologic abnormality. (Fig. 4.)

The remaining two cases from the Pennsylvania Hospital illustrate this type of lesion. The first of these patients had a history of long-stand-

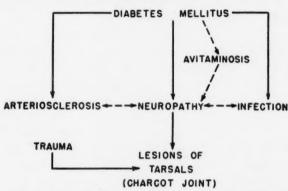


Fig. 3. Diagram of the pathogenesis of the Charcot type of bony lesion in the feet of diabetics. Solid lines indicate well established relationships; broken lines show more tenuous ones.

ing infection, arterial insufficiency and roentgen ray evidence of phalangeal lesions in the left foot, as well as physical signs of advanced diabetic neuropathy and abnormalities of the Charcot type in the right foot.

CASE III. S. J., an unemployed forty-nine year old Negro male, was referred to the Dermatology Clinic of the Pennsylvania Hospital in 1937 with a history of having had a genital sore six weeks previously and a maculopapular rash of one week's duration. Serologic tests for syphilis were positive and treatment was initiated but not completed because of the patient's failure to return. Urine tests for sugar at that time were negative

at that time were negative.

In 1940 he was seen in the Medical Clinic with complaints of vague epigastric distress. Gastric analysis and upper gastrointestinal x-ray studies revealed no abnormalities. The blood serologic tests for syphilis were negative. Urinalyses were positive for sugar and a fasting blood sugar was 291 mg. per cent. The patient denied any of the usual symptoms of diabetes mellitus and was not aware of any diabetes in his family. Again, the patient failed to keep any further clinic appointments and he was not seen until May, 1947, when he was admitted to the surgical service with an infected ulcer over the left medial malleolus. During the seven-year interval he had followed no special diet and had taken no insulin. The urine on admission contained sugar and a fasting blood sugar was 255

mg. per cent. Other studies were negative, including serologic tests for syphilis. His diabetes was controlled on a 2,100 calorie diet containing 110 gm. of protein, 200 gm. of carbohydrate and 45 gm. of fat, and 40 units of protamine zinc insulin daily. A skin graft

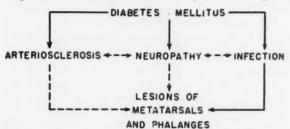


Fig. 4. Diagram of the pathogenesis of the infectious-vascular type of bony lesion in the feet of diabetics. Solid lines indicate direct relationships; broken lines indicate indirect or less well established ones.

partially corrected the ulcerated area following eradication of infection by local applications and parenteral penicillin. He was discharged to the outpatient department where he was followed up for two months, during which time his diabetes was controlled well but the ulcer failed to heal completely in spite of repeated sympathetic blocks and various types of local applications.

He was readmitted to the hospital for a left lumbar sympathectomy. His diabetes remained under good control and postoperatively circulation in the left leg seemed improved and the ulcer gradually healed. Thereafter, the patient was followed up in the outpatient department for fourteen months. His diabetes was poorly controlled, largely because he did not adhere to the prescribed diet. The dosage of insulin varied between 46 and 66 units of globin insulin daily. The left foot remained warmer and drier than the right, with good arterial pulsations palpable bilaterally.

At the end of that period he was readmitted because of an infected ulceration at the base of the left fourth toe, with cellulitis and edema of the entire foot. Physical examination was otherwise unchanged. At that time the pupils reacted normally to light and accommodation. On local applications and intramuscular penicillin the lesion began to heal slowly. Control of the diabetes was achieved and maintained with the previous diet, and 58 units of protamine zinc insulin and 19 units of regular insulin were administered separately every day. During that admission laboratory studies, including serologic tests for syphilis, were negative.

Two months after discharge from the hospital the patient once more failed to keep clinic appointments. As was learned later, the lesion healed but his diabetes again relapsed into a poorly controlled state. Four months later he came to the accident ward complaining of swelling and pain in his right ankle. Inadequate x-ray examination revealed only some calcification of a peripheral artery but no fracture or dislocation. However, the swelling persisted with progressive painless deformity without limitation of usage. He allegedly continued to take 24 units of regular insulin and 34 units of protamine zinc insulin daily until early in January, 1950, when he stopped insulin entirely. On April 27, 1950, he noted a break in the skin of the left foot with ensuing pain, tenderness and local swelling. He was readmitted to the hospital on March 1, 1950, at which time physical examination was generally unchanged. Pupillary reactions to light were normal. Ophthalmoscopic examination revealed moderate arteriosclerosis, linear hemorrhages and waxy exudates. The edge of the liver descended two fingerbreadths below the right costal margin on deep inspiration. Normal dorsalis pedis and posterior tibial artery pulsations were palpable bilaterally. There was a grossly infected fissure between the right fourth and fifth toes, with a vesicle over the lateral aspect of the right foot which was swollen. The patellar and Achilles tendon reflexes were absent on the right and diminished on the left. Vibration perception was diminished below the knees. Tenderness over the right posterior tibial nerve was elicited.

The urine on entry contained abnormal amounts of albumin, sugar and acetone, with a few hyaline casts, 4 to 8 erythrocytes, and a rare leukocyte per high power field. The hemogram was normal. A serum uric acid level was 5.0 mg. per cent. Total serum cholesterol and cholesterol ester values were 168 and 114 mg. per cent, respectively. Serologic tests for syphilis were negative. Lumbar puncture revealed clear colorless spinal fluid with normal pressure and dynamics, 1 neutrocyte and 80 erythrocytes per cu. mm., a protein of 0.04 gm. per cent, a negative Wassermann test and a colloidal gold curve of ten zeros. Roentgen ray films of the spine were normal but films of the feet revealed the following abnormalities: on the right (Fig. 5A) diffuse changes at the proximal ends of the metatarsals and in the distal tarsal row, with frayed, fuzzy bone margins, loss of cortical substance and total obliteration of the intervening joint spaces, especially the tarsometatarsal joints and the articulations between the first, second and third cuneiform bones; on the left (Fig. 5B) discontinuity in the mid-portion of the proximal phalanx of the fourth toe and narrowing of the fifth terminal phalanx, with normal tarsal bones and articulations.

On the third hospital day the right foot was incised along its lateral border and considerable purulent drainage ensued, culture of which revealed mixed bacterial flora. On antibiotic therapy, local applications and general supportive measures the foot healed slowly. The patient's diabetes was controlled on a 2,100 calorie diet, containing 110 gm. protein, 95 gm. fat and 200 gm. carbohydrate, and 24 units of

protamine zinc insulin daily.

The patient was discharged on April 17, 1950, and was followed up in the outpatient department. He did not adhere to his diet, took insulin irregularly and tested his urine infrequently. On November 28, 1950, the patient lacerated his right third and fourth toes and four days later re-entered the hospital. There was cellulitis of the dorsum of the right foot with paronychia of the right third and fourth toes and a 7 mm. circular area of black crust at the tip of the fourth right toe with suppuration beneath it. Both feet were warm and moist and the pedal pulses were present bilaterally. There were numerous superficial varicosities of both legs. The area of cellulitis was incised and the nails from the third and fourth right toes were avulsed with liberation of purulent material. The lesions healed satisfactorily with antibiotic therapy and local applications, paravertebral blocks on the right, ligation of the right superficial femoral vein and general supportive measures. The diabetes mellitus was easily controlled with a 2,500 calorie diet made up of 120 gm. protein, 230 gm. carbohydrate and 122 gm. fat. His insulin dosage was 28 units of regular insulin and 14 units of protamine zinc insulin mixed daily. The patient was discharged and is being followed up in the outpatient department clinic, where he continues to ignore his diabetic regimen.

The final patient had a long history of chronic infection and vascular impairment with typical metatarsophalangeal lesions in the right foot, with the subsequent development of neuropathic signs and tarsal changes in the same foot.

Case IV. R. T., a colored housewife, was



Fig. 5. Case III. A, right foot; Charcot type of changes of the tarsal area. B, left foot; note destructive changes in the phalanges of the fourth and fifth toes.

first admitted to the Pennsylvania Hospital at the age of forty-three, giving a history of having had diabetes mellitus for several years during which time she followed no special dietary program and took no insulin. The past medical history was otherwise negative. No history of venereal disease or antiluetic therapy was elicited.

Approximately three years before entry she experienced intermittent swelling of the feet and ankles. About one year prior to entry she first noted a small nodular lesion on the right fifth toe which failed to regress. Six months later an ulcerated lesion developed on the dorsum of the right foot which healed slowly. Three months before entry the right foot became more enlarged than the left and the lesion on the fifth toe became larger and more tender. She noted numbness of the right great toe, began to walk on a wide base and experienced great difficulty in maintaining equilibrium in the dark. About the same time anorexia, thirst, polydipsia, polyuria and decreased visual acuity developed, and she began to lose weight. The right fifth toe became inflamed; four days before entry the family physician incised the toe, obtaining purulent material. A blood sugar, non-fasting, two days later was 285 mg. per cent.

Physical examination on admission the following day revealed a moderately obese adult colored female with signs of a recent loss of weight. The pupils reacted normally to light and ophthalmoscopy revealed slight arteriovenous nicking as the only abnormality. A soft systolic murmur was audible at the cardiac apex. The chest and abdomen were otherwise normal. The blood pressure was 125 mm. Hg systolic and 89 mm. diastolic. The right foot was enlarged and warmer than the left with an acutely inflamed tender fifth toe bearing a draining incisional wound on the medial surface. There were hyperesthesia and hyperalgesia over the right great toe and sluggish knee jerks bilaterally. The pedal pulses were easily palpable throughout and the skin temperature of the left foot was normal.

Urinalysis on entry was negative except for 3 plus reactions for albuminuria and a 1 plus



Fig. 6. Case IV. Right foot; the fifth toe has been amputated surgically. Notice the marked destruction in the metatarsal and phalanges of the fourth toe as well as the periosteal proliferation along the third metatarsal and the early changes of the Charcot type in the distal tarsal row.

reaction for glycosuria. The hemoglobin concentration was 12.5 gm. per cent and the erythrocyte, leukocyte and differential counts were normal. A blood urea nitrogen level was 14 mg. per cent, serum protein 6.8 gm. per cent. Serologic tests for syphilis were negative. A culture of the purulent drainage from the right fifth toe produced an abundant growth of hemolytic streptococci and diphtheroids.

The diabetes was controlled by a small dose of regular insulin and equal feedings every six hours. The lesion on the toe failed to respond to conservative treatment. The toe was amputated, pathologic examination revealing tissue necrosis, leukocytic infiltration and marked sclerosis of the smaller arteries. The amputation site healed slowly in response to potassium permanganate soaks, zinc peroxide dressings and sulfadiazine by mouth. The patient was

returned to the care of her family physician with recommendations for therapy including a 1,380 calorie diet containing 60 gm. protein, 60 gm. fat and 150 gm. carbohydrate, and 23 units of protamine zinc insulin daily.

The patient was next seen nearly six years later, at which time an interval history revealed the development of hypertension four years previously, with bilateral ankle edema and exertional dyspnea for one year. She had neglected her diet and had taken insulin only for short periods of time at long irregular intervals. Six months prior to re-entry her right foot had become progressively larger and discolored. Three and a half weeks before entry the foot became painful. Her family physician treated her with penicillin and bed rest; the acute pain subsided but the foot remained enlarged, discolored and tender to pressure. Two weeks prior to entry gradually progressive orthopnea, paroxysmal nocturnal dyspnea, anorexia, irregular bowel movements, post-prandial abdominal distention and urinary frequency developed. She had been digitalized by her family physician during that period with some improvement.

On entry the patient weighed 132 pounds (60 kg.). The body temperature and pulse rate were normal; blood pressure was 180 mm. Hg systolic and 85 mm. diastolic. Bilateral lenticular opacities obscured the ocular fundi; the pupils reacted sluggishly to light. There were no avitaminotic stigmas of eyes or tongue. The lung fields were clear except for bilateral basilar medium crepitant rales; the heart was grossly enlarged to the left with a harsh blowing systolic murmur audible over the entire precordium and there was a loud aortic second sound. The abdomen was normal except for an enlarged non-tender liver descending four fingerbreadths below the right costal margin. The right foot was enlarged and mildly tender throughout but there were no open lesions. The dorsalis pedis pulsation was barely palpable but anterior and posterior tibial pulsations were normal. The skin was dry, scaling and darkened, with cool toe tips. The fifth toe was absent with a well healed amputation site. The left foot was normal with good pulses throughout. There was a trace of pretibial edema bilaterally. Neurologic examination revealed diminished vibration sense and hypalgesia over both lower legs, with absent vibration sense and analgesia in both feet. The patellar and Achilles tendon reflexes were absent bilaterally.

Urinalyses showed specific gravities of 1.010 to 1.016, persistent albuminuria and 10 to 15 erythrocytes and many leukocytes in the sediment. The hemoglobin concentration in the blood was 8.0 gm. per cent. Leukocyte counts ranged from 8,400 to 15,100 with normal differential counts. The blood urea nitrogen concentration was 15 mg. per cent with a total protein of 6.8 gm. per cent, total cholesterol of 221 mg. per cent, cholesterol esters of 107 mg. per cent and a uric acid of 5.3 mg. per cent. Serologic tests for syphilis were negative. A phenolsulfonphthalein test showed no dye excretion in twenty minutes and a total excretion of 15 per cent in two hours. An electrocardiogram showed left axis deviation and flattened T waves in all leads. X-ray examination of the right foot (Fig. 6) showed marked osteoporosis of the third metatarsal bone with some bone destruction and periosteal proliferation at the base. There was destruction of the entire fourth metatarsal bone and the proximal segment of the adjacent phalanx with periosteal proliferation as well as some thinning of the mid-shaft of the third proximal phalanx. The fifth toe was missing. In addition, there were noted moderate destructive changes of the distal tarsal row, their interarticular surfaces and the tarsometatarsal joint lines. X-ray examinations of the left foot, the chest and upper gastrointestinal tract revealed no abnormalities.

The diabetes was easily controlled with a 2,500 calorie diet containing 120 gm. protein, 200 gm. carbohydrate and 135 gm. fat in four equal feedings given, with 12 units of regular insulin at six-hour intervals. The signs of myocardial failure subsided on bed rest, digitalis and mercurial diuretic therapies. An incision into the lateral aspect of the right foot failed to identify any localized infection.

A right-sided sympathetic block at L1, 2 and 3, with 1 per cent procaine, caused a definite increase in warmth over the right leg but produced no perceptible change in the temperature of the foot. Buerger's exercises, priscoline® therapy and a course of procaine penicillin failed to alter the condition of the foot.

She was returned again to the care of her family physician at which time her diabetes was controlled by a 2,100 calorie diet containing 110 gm. protein, 200 gm. carbohydrate and 95 gm. fat in three meals and a bedtime feeding, and 36 units of protamine zinc insulin and 12 units of regular insulin mixed daily.

### CONCLUDING REMARKS

In view of the usually excellent correlation in these four patients, and other similar ones, between the duration and severity of diabetic neuropathy and the development of changes in the bones of the ankle and their articulations

TABLE I\*

CHARACTERISTICS	CHARCOT TYPE	INFECTIOUS VASCULAR TYPE
DONES AFFECTED	TARSAL BONES AND THEIR ARTICULATIONS, AND ADJACENT METATARSAL, TIBIAL AND FIBULER SURFACES	PHALANGES AND METATARBALS, PARTIGULARLY THEIR SHAFTS
DURATION OF DIABETES	LONG - STANDING	NOT SIGNIFICANT
SISMS AND SYMPTOMS OF DIABETIC HEUROPATHY	SEVERE	MINIMAL OR ABSENT
SOFT TISSUES	ABSENT	PRESENT, USUALLY CHRONIC
SIBNS OF ARTERIAL WEUFFICIENCY	MINIMAL OR ABSENT	MODERATE TO SEVERE

\*The differentiating characteristics of the Charcot type of bony change in the feet of diabetic patients, as compared with those of the infectious-vascular type.

similar to those described in Charcot joints due to other diseases, there would seem to be little doubt as to the cause and effect relationship between the neuropathy and these particular bony changes. The nature of this relationship is not clearly defined nor is the manner in which diabetes initiates the entire process.

The pathogenesis of the second type of lesion may be more open to question. Such lesions of the phalanges and metatarsals are not reported, to our knowledge, in non-diabetic patients with Charcot joints due to syphilis and syringomyelia in the absence of infected ulcerations or other sepsis. In addition, x-ray changes similar to those described do occur in the feet of otherwise well patients with pyogenic soft tissue infections following puncture wounds and other secondarily infected trauma, with extension to the periosteum and bone as an osteitis or early osteomyelitis. Similarly, atrophic changes have been found in the distal bones of the foct as a result of vascular insufficiency due to arteriosclerosis of the endarteritis obliterans type alone, without accompanying infection or neuropathy. That these facts may be applied in explaining similar lesions in diabetics is illustrated by Cases III and IV above.

The differentiating characteristics of the two types of lesions are summarized in Table 1.

### SUMMARY

1. Patients with diabetes mellitus may develop destructive lesions of the bones of the foot,

demonstrable by roentgen ray examination, of two types: gradual dissolution of the tarsal bones and their articulations (the Charcot joint), attributable to diabetic neuropathy; rarefaction of the phalanges and metatarsals secondary to chronic infection in the adjacent soft tissues and arterial insufficiency.

2. Four illustrative cases of Charcot joint in diabetes mellitus are reported, two of which showed, in addition, the second type of bony

lesion.

### **ADDENDUM**

Since the submission of this paper for publication two additional cases of neuropathic joints occurring in diabetic patients have been reported.18 The involved foot of each patient showed both of the types of lesion described before, with appropriate collateral historical and physical findings. Their improvement following lumbar sympathectomy is interesting in that the procedure not only ameliorated the changes due to infection and circulatory disturbances but also apparently halted the progress of the Charcot type of abnormality. The bibliography includes three cases of Charcot joints in diabetics not found by us. 19-21

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# A New Liver Extract Derived from Pregnant Mammalian Liver\*

I. Its Effect on Peripheral Neuropathy

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The problem of peripheral neuropathy in the diabetic has been a subject of much concern to us for many years. It has been particularly disturbing, first, because of the large incidence of this complication in diabetes mellitus and second, because therapy with all known antineuritic factors present in vitamin B complex had proved to be disappointing. It was only after the addition of crude liver or preparations of vitamin B complex derived from natural sources (usually containing liver) that we began to see evidence of a somewhat better therapeutic result in the treatment of this complication. <sup>2</sup>

This led us to suspect that liver probably contained some still unidentified fractions which possessed greater therapeutic potentialities in the treatment of diabetic neuropathy than any of the known components. With this premise in mind we proceeded to make liver extract by a technic aimed at retaining many of the substances known to disappear by the methods previously used to prepare the crudest liver extracts. In evaluating a variety of liver sources we found that liver from pregnant mammals yielded a preparation of highest clinical potency. Thus evolved a water-soluble extract which was transparent, amber colored and possessed rather unique clinical and physiologic properties. After having determined by long-term toxicity studies in rabbits and rats that this extract had no deleterious effect, we decided to evaluate the material in patients with diabetic neuropathy.

The series consisted of a group of diabetics who presented one or more of a variety of symptoms and signs that are accepted as part of the symptom-complex of diabetic neuropathy. Among these symptoms could be listed the

following: peripheral numbness, tingling, sticking pains, pins and needles sensations, drawing pains in the legs, burning sensations in the toes or feet, stiffness in the extremities, and burning tongue. Also included were effects upon the central nervous system producing such symptoms as crying spells, depressions, agitation and vertigo. Those symptoms of visceral neuropathy related to involvement of the autonomic nervous system included anorexia, belching, diarrhea and urinary incontinence.

The cases of peripheral neuropathy revealed, among the more common objective findings in the distal aspect of the limbs, reduced vibratory sense, hypesthesia, anesthesia and reduced response to thermal stimulation. They also showed reduction or loss of deep tendon reflexes, especially in the lower extremities, reduced motor power in the limbs and occasionally interosseous and thenar atrophy. When symptoms of visceral neuropathy such as diarrhea were present, x-ray of the gastrointestinal tract revealed distortions in small bowel pattern, i.e., isolated areas of local distention and "puddling."

Treatment consisted of the daily intramuscular injection of 5 cc. of pregnant mammalian liver extract (PMLE). † In most cases the injections were continued for two weeks. The injection was practically painless, produced no local irritation and no constitutional reaction. There were, however, three patients who developed mild local allergic reactions after one week of daily therapy.

The series consisted of 127 diabetics with manifestations of neuropathy. It is interesting to note

<sup>†</sup> For purposes of brevity the pregnant mammalian liver extract will hereinafter be referred to as PMLE in this paper.

<sup>\*</sup> From the Diabetic Research Laboratory and Medical Services of the Maimonides Hospital, Brooklyn, N. Y.

that 94 per cent experienced reversibility of symptoms. (Table I.) Of this group 84 per cent showed good to excellent results and 10 per cent had a fair result. Six per cent of the series failed to show any response to this therapy. In some of the patients evidence of improvement

Table I
RESULTS OF TREATMENT OF PERIPHERAL DIABETIC
NEUROPATHY WITH AN EXTRACT FROM PREGNANT
MAMMALIAN LIVER

Results	No. of Cases	Per cent
Excellent	56	44
Good	50	40
Fair	14	10
Failures	7	6
Total	127	100

was manifested within two hours of the time of injection. In those patients who had good to excellent results, remission in the clinical symptoms occurred within a week after the institution of treatment.

The objective manifestations of reversibility were certainly not as striking as the subjective symptoms. While improvement in vibratory sense could be detected quantitatively, this reversibility first became evident two to four weeks after therapy was started. Disturbances in tendon reflexes seemed to be irreversible as were also the muscle atrophies.

Patients in whom diarrhea was an outstanding manifestation of visceral neuropathy and in whom no organic basis for this symptom could be established were relieved within one week after institution of treatment.

### CASE REPORTS

Case I. M. K., a thirty-nine year old female diabetic, first came under observation on October 17, 1949. She stated that eighteen months previously she had sought medical aid for a severe pain in her left leg. At the same time she also complained of oral dryness, urinary frequency and weight loss. It was found on investigation that she was suffering from diabetes mellitus. She was placed on a maintenance diet and was given 40 units of protamine zinc insulin daily. Her diabetic symptoms promptly abated. However, in spite of the satisfactory control of her diabetes she continued to com-

plain of the severe pain in her left leg. This pain occurred in paroxysms and would last for periods of three months. The patient would then experience relief for one to two weeks and then suffer a recurrence. As time went on the relapses of left lower extremity pain became more severe and longer lasting with relatively shorter intervals of relief. At no time, however, did the patient experience complete freedom from pain. She was investigated at the Neurological Institute in New York and was under observation in the Presbyterian Hospital with numerous orthopedic and neurologic consultations. These examinations revealed a normal gait in all phases. There was weakness in the left lower extremity, especially in the flexors of the thigh. General motor co-ordination was good, nonequilibratory co-ordination tests were normally performed. Test acts and speech were normal. There was generalized hyporeflexia. Abdominal reflexes were present and equal. No pathologic reflexes were elicited. There were no signs of meningeal irritation and the sensory system appeared intact. The cranial nerves were normal. During this period of observation the diagnosis of herniated intervertebral disc was considered. When no satisfactory positive evidence of a herniated disc was established, the patient was discharged with a final diagnosis of diabetes mellitus and diabetic neuropathy of the left sciatic nerve. She left the hospital unimproved and continued to experience the same episodes of severe left lower extremity pain starting in the region of the buttock and radiating along the posterior aspect of her extremity as far as the heel. On discharge from the hospital the patient was advised to continue with the use of large doses of brewer's yeast and thiamine chloride.

The patient came under our observation one year later with the story of severe left lower extremity pain of such degree as to confine her continuously to bed and to necessitate the use of narcotics for relief. On October 17, 1949, we started treatment with PMLE, giving her 5 cc. intramuscularly daily for two weeks. The patient did not show any manifestations of relief until the seventh injection, following which she showed progressive improvement so that one month after the beginning of treatment she was entirely free of symptoms. The patient did not receive any other therapy. She has been observed every three months since the initial course of treatment and on April 24, 1951, one

and a half years later, she was still in complete remission. She has not required any additional therapy.

CASE II. C. F. is a thirty year old male who has had diabetes for the past four years. He has been well controlled with a diet consisting of 230 gm. of carbohydrate, 125 gm. of protein and 100 gm. of fat, with 25 units of protamine zinc insulin. In December, 1950, he first experienced symptoms of peripheral neuropathy consisting of severe burning pain of the toes. Examination at that time revealed no abnormal neurologic signs except for moderate diminution in vibratory sense perception. 3,4 These symptoms were quite severe and annoyed him especially while he was working. He was given 5 cc. of PMLE intramuscularly daily for eight days. The burning of the feet was completely gone after the third injection. He was reexamined two and one-half months later and was found to be in a complete remission.

CASE III. L. H. is a fifty-four year old female who had been diabetic for ten years. She had been treated by diet and had not received any insulin during this period. When first seen she was spilling 4 per cent sugar in her urine and her blood sugar was 279 mg. per cent. She was given a diet consisting of 150 gm. of carbohydrate, 75 gm. of protein and 90 gm. of fat, and was instructed to take 20 units of protamine zinc insulin daily. Two weeks after starting insulin she noticed tingling sensations in her toes. These persisted and a few months later she began to experience severe tingling of her hands and of the anterior aspect of her chest wall. It is interesting to note that these symptoms developed after starting insulin therapy and at the time that her diabetes came under control. This has been a not uncommon observation. Neurologic examination proved to be non-revealing except for reduced response to vibratory sense stimulation. She was started on our liver extract on September 13, 1950, and was given 5 cc. intramuscularly every day for a total of seven days. She reported that the tingling in her left hand, which was very severe, was greatly alleviated twenty-four hours after the first injection. After the sixth injection all her complaints of tingling in her hands and feet had completely disappeared and the tingling sensations in her chest were very slight. She was observed periodically for the next six months and at the time of her last examination her neuropathic symptoms were still in complete remission.

Case IV. S. T. is a thirty-seven year old male who was diabetic for the past thirteen years. The onset was sudden with classic symptoms consisting of polyuria, thirst, weakness and weight loss. He has been moderately well controlled for the entire period with use of 70 units of insulin a day and a diet consisting of 240 gm. of carbohydrate, 100 gm. of protein and 100 gm. of fat. In July, 1941, he first began to experience bouts of diarrhea. At first they occurred only occasionally but soon became more frequent, recurring about twice a month. The bouts were characterized by abdominal cramps and diarrhea lasting one or two days. Extensive gastrointestinal investigations were carried out during three hospital admissions without revealing evidence of organic intestinal disease. Sigmoidoscopy showed a normal mucosa and wet smear failed to reveal any pus. In October, 1950, he developed one of his worst bouts of diarrhea, consisting of four to five movements a day with severe abdominal cramps. After this condition had persisted for three months he was started on our liver extract. He was given 5 cc. intramuscularly daily and noticed after the third injection that the diarrhea stopped for the first time in three months. After completing two weeks of therapy a period of constipation followed for four days, and then normal bowel habits returned. This is an example of visceral neuropathy in a diabetic showing a good response to PMLE.

CASE v. R. S. is a thirty-seven year old white male who has been diabetic for the past seven years. When first seen two years ago he complained of severe, constant shooting pain in both legs. He also complained of tingling pain in his toes. These symptoms were worse during the night; they were so severe that they kept him awake a good part of the night. They had become progressively worse in the past six months. Neurologic examination revealed diminution in some sensory responses including pain, touch and vibration sense in the lower extremities. Knee jerks and ankle jerks were reduced. There were no other significant neurologic findings. The diabetes was well controlled on a diet consisting of 170 gm. of carbohydrate, 100 gm. of protein and 90 gm. of fat, with 50 units of insulin per day. He was given 5 cc. of PMLE daily for a period of two weeks at the end of which time he first noticed that the tingling sensations in his legs improved somewhat. Administration of the extract was then continued

twice a week for a month. By this time the shooting pains had completely disappeared but the tingling sensations in his toes, although improved, persisted for another month. After the patient was relieved of all his symptoms, therapy was discontinued. Six months later he was still in complete remission.

CASE VI. R. G. is a sixty-four year old white female who had been diabetic for the past twelve years. When she first came under observation five years ago, she related that besides the thirst, frequency and weight loss which was attributed to a deterioration in her carbohydrate tolerance, she had been experiencing for three months a cramp-like pain in the calf of her left leg on walking one-half block which was quickly relieved by rest. This symptom proved to be the result of an arterial impairment in her left lower extremity and was thought to be caused by arteriosclerosis obliterans. She also complained of coldness in her feet and numbness in her toes. Study of her peripheral circulation revealed moderate impairment of blood flow in the left leg with loss of pulses below the knee. The pulsations in her right lower extremity were normal. Oscillometric readings at this time were as follows: right leg below the knee, 4; above the ankle, 1; in the left leg the readings were: below the knee, 1; above the ankle, 0. Four years later while under observation, the patient suddenly experienced an attack of severe pain in the right lower extremity. She observed at this time that the intermittent claudication in her right leg was worse than in the left leg. In addition, she developed severe burning pain in the right foot and toes which was present continuously at rest and worse during the night. When she walked she felt as though there were pebbles in her shoe. She also complained of sensations which she described as insects crawling on the skin of her leg. Examination at this time revealed evidence of profound impairment of blood flow in the right lower extremity. The extremity was cold and pulseless below the level of the knee and the foot assumed a dusky cyanotic hue in dependency. Oscillometric readings gave the following results in the right leg:  $\frac{1}{2}$  below the knee and 0 above the ankle. It was obvious that the patient had developed a thrombosis in the right popliteal artery. On observing a loss in pain, touch and vibration sense in the toes of the right foot, with evidence of a right dropped foot, it became apparent that the patient also had an ischemic neuritis arising

from her circulatory impairment. Although recognizing that this type of neuritis is pathogenetically different from metabolic neuropathy, an attempt to evaluate PMLE therapy was made. The patient was given 5 cc. of the extract intramuscularly daily for a period of three weeks without any measurable relief of symptoms. This failure to respond is comparable with the experience which we have had in other cases of ischemic neuritis.

CASE VII. F. R. is a white fifty-one year old female who has had diabetes for the past twelve years. The condition was well controlled with a diet consisting of 200 gm. of carbohydrate, 75 gm. of protein and 65 gm. of fat, and the daily use of 68 units of insulin. One year ago she started to complain of numb sensations of the right foot extending from the toes to the ankle. This symptom persisted during the entire year. No abnormal neurologic findings were observed except for a reduction in vibratory sense in the toes of both feet, more marked in the right. She was given PMLE therapy in doses of 5 cc. intramuscularly daily for a week. At the end of the third injection all her symptoms disappeared completely. She has been in complete remission for the past month.

CASE VIII. P. P. is a sixty-three year old female who first came under observation on January 8, 1950. She was discovered to be diabetic while being treated in a hospital for an attack of acute gallbladder colic six months previously. The finding of the diabetes was made in the course of a routine examination and in the absence of diabetic symptoms. She now complained, however, of weakness and weight loss since she had been subjected to dietary restrictions. Examination revealed the presence of 0.6 per cent glucose in her urine and a fasting blood sugar of 193 mg. per cent. In order to relieve her of her symptoms she was provided with a diet consisting of 175 gm. of carbohydrate, 70 gm. of protein and 60 gm. of fat and was given 15 units of protamine insulin every morning before breakfast. Her diabetes came under control quickly and on examination six weeks later her urine was negative and the fasting blood sugar was 110 mg. per cent. She appeared again for examination eight months later at which time she stated that for a period of four months since July, 1950, she had experienced numbness, sticking pain, throbbing and sensations of pins and needles on the right side of her face. These symptoms were of sufficient severity to require the use of narcotics for relief. Examination revealed evidence of hypesthesia and hypalgesia of the skin innervated by the middle branch of the right fifth nerve. A diagnosis of neuritis of the right fifth nerve was therefore entertained. She was given 5 cc. of PMLE intramuscularly daily for the next two weeks. After the third injection the patient noticed slight subsidence of her symptoms and at the end of the two-week period she was totally relieved of all the neuropathic symptoms in the right side of her face. When re-examined three months later she was found to be entirely free of symptoms and on examination six months after the institution of PMLE therapy she was still in complete remission.

Case IX. R. H. is a young adult male who first came under observation on February 6, 1944, when he was twenty-four years of age, with a history of having been diabetic since the age of twenty-one. He proved to be a severe diabetic, for in order to provide him with his physiologic needs in his diet with minimal glycosuria, it was necessary for him to take 100 units of insulin a day. He was entirely asymptomatic. He was seen periodically three to four times a year.

In September, 1950, he experienced the sudden onset of numbness involving all the digits of his right hand. This symptom persisted and became progressively worse until he was seen two months later. In the absence of any positive neurologic findings except a reduction in perception of vibration sense in all four extremities, it was considered that this was peripheral neuropathy of diabetic origin. He was given 5 cc. of PMLE intramuscularly for one week. All complaints of numbness disappeared twenty-four hours after the first injection. When seen five months later he was still in complete remission.

CASE X. L. R. is a sixty-one year old male who had been treated for diabetes for the past three years on a diet consisting of 1,800 calories with 250 gm. of available glucose. He was satisfactorily controlled with 45 units of insulin a day. His glycosuria was minimal and fasting blood sugars ranged between 140 to 160 mg. per cent. He was normotensive and presented no positive pathologic findings. The patient was asymptomatic until four months ago when he started to complain of shooting pains on the outer aspects of both thighs radiating to the legs. He also complained of burning pain and tingling

in the toes of both feet. There was no evidence of any peripheral arterial disease.

Neurologic examination revealed reduction in pain, touch and vibratory sense in the feet and diminished knee jerks and ankle jerks. A diagnosis of diabetic peripheral neuropathy was made and the patient was given 5 cc. of PMLE intramuscularly daily for 10 doses. There was complete subsidence of his neuropathic symptoms after the third injection. When seen four months later he was still in complete remission.

### COMMENT

We recognize that evaluation of a therapeutic agent is difficult and full of pitfalls when one must rely largely upon the patient's subjective responses as a criterion. This situation unfortunately obtains in dealing with neuropathies of metabolic origin. In order to provide adequate controls in this study, the following precautions were taken: (1) Long-term observations were carried out during the pre-treatment period and no patients were used in whom neuropathic symptoms had not been present for at least two months. (2) Nothing else was given except our extract for the treatment of the neuropathy. (3) The patients did not know the purpose of the therapy or what was given except in so far as they were apprised that it was part of the treatment for the diabetes. (4) No pointed questions were aimed at the patients during the period of observation; evaluation of symptoms was based upon the voluntary reports of the patients. (5) Some double-blindfold tests were carried out in which neither the patient nor the person administering the material knew what was given. Placebos consisting of distilled water stained with acriflavine were employed in these blindfold tests. (6) Material was supplied to another observer, Dr. I. M. Rabinowitch of the Montreal General Hospital, who consented to conduct a completely independent evaluation of our extract.5

The therapeutic effects which we have observed are probably derived from components not previously isolated from liver. The failure of this extract to produce reticulocytosis is presumptive evidence that the potent antineuritic properties of our extract are not ascribable to vitamin  $B_{12}$  or folic acid. Furthermore, analysis of our extract revealed the presence of only 0.09 microgram of vitamin  $B_{12}$  per ml. and 0.15 microgram of folic acid per ml. These trace

quantities obviously play no therapeutic role in the neuropathies.

Administration of the extract had no effect upon carbohydrate tolerance.

Long-term toxicity studies performed in rabbits and rats have failed to reveal any deleterious effects of the extract. Rabbits have been injected with fifty times the human dose per unit weight daily for four months without any evidence of toxicity. We have also given two hundred times the human dose per unit weight intravenously to rabbits without any deleterious effect.

It is interesting, too, that a two-week course of therapy usually suffices to produce a remission lasting between two and six months. Resumption of therapy during the relapse generally effects a prompt remission comparable with that of the initial therapy. We have found that when there is a tendency for relapses to occur the administration of one dose of our extract once a week serves to maintain the patient in continuous remission. Prolonged remissions have now been observed for as long as two years.

### CONCLUSION

A new extract\* derived from pregnant mammalian liver is described which has the property of reversing the symptom complex of diabetic neuropathy.

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<sup>\*</sup> The material used in this study was kindly supplied in part by Dr. Norbert Fell of the International Biochemical Corp., Brooklyn, N. Y.

# Experiences with a New Liver Extract for the Treatment of Diabetic Neuropathies\*

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THE purpose of this communication is to report the experiences with the first twenty cases of diabetic neuropathies treated with the pregnant mammalian liver extract† developed by Dr. W. S. Collens and his associates.<sup>1</sup>

There are few illnesses that can be more disabling than a diabetic neuropathy; addiction to morphine from persistent and intolerable nocturnal pain, paralysis of an upper or lower extremity, incontinence of urine due to "diabetic cord bladder" and nocturnal incontinence of feces are examples. The number of such severe cases is not large but the total incidence of diabetic neuropathies is much higher than that reflected in the literature when consideration is given to manifestations which are insufficient for the patient to complain about but which may be elicited after careful questioning. Slight numbness or tingling of a finger or two, or stiffness of an arm or leg on awakening and which disappears soon after, are examples. The high incidence of parasthesias is suggested from their frequency in well established cases of diabetic neuritis. In the writer's experience it is about 85 per cent, which fits in with the 70 per cent incidence noted by Jordan<sup>2</sup> and the fortyone of fifty cases (82 per cent) reported by Joslin.3

Much as is known of the neuropathies of diabetes mellitus, there is much, as yet, to be known of their pathology. To Jordan's very satisfactory working classification<sup>2</sup> of symptoms—hyperglycemic, circulatory, degenerative and neuritic—there are, as the writer has shown,<sup>4</sup> those due to achlorhydria. From the standpoint of response to treatment, the hyperglycemic and the achlorhydric group are the least troublesome. More difficult are the cases of typical diabetic neuritis particularly those with an elevation of spinal fluid protein which, as a rule,

parallels the increase and decrease of the severity of the symptoms. Most resistant to all forms of therapy are the vascular and degenerative types.

No form of therapy for any illness is uniformly successful. It is gratifying, however, to be able to report satisfactory response to treatment with this new liver extract in all of the previously mentioned types of cases. In fact, among the first twenty patients treated, in two only has complete relief of symptoms not been noted. Whether there has been any improvement at all in these two cases is difficult to determine because of the unreliability of the statements due to associated psychic disturbances. Both have mental depression which, although a manifestation of diabetic neuropathy and might therefore be expected to reflect improvement with the extract or otherwise, is out of all proportion to the physical discomfort and thus does not appear to be due entirely to a diabetic neuropathy.

A difficulty in determining a causal relationship between treatment and improvement of diabetic neuritis is the limited usefulness of objective signs. As is well known, in early cases of typical diabetic neuritis there may be very severe pain in a leg or in an arm with no objective neurologic signs. In the "vascular" group there may be intolerable "burning" of the feet with no objective neurologic signs. Adding to these difficulties in the interpretation of improvement is the disappearance of symptoms at times without any treatment. Also, with control of the diabetes alone there may be rapid improvement of symptoms of the hyperglycemic type of disturbance and, as was shown by the writer,4 equally rapid may be the improvement after correcting the gastric acidity in the achlorhydric type of disturbance. In this investigation, therefore, since the criteria of the effectiveness of the extract were to be the sub-

<sup>†</sup> To be referred to hereafter as PMLE.

<sup>\*</sup> Delivered before the Second International Gerontological Congress, September 12, 1951, St. Louis, Mo.

jective improvements, no cases were included in which the symptoms had not been constant and severe for at least two months, despite control of the diabetes; in cases of achlorhydria or hypochlorhydria despite correction of the gastric acidity, and despite the usual measures otherwise employed, physiotherapy, etc.

Among the cases to be reported here are two with "diabetic cord bladder," a case complicated by a pressure palsy of a hand with some atrophy of the interossei muscles, one with advanced generalized vascular disease, a non-healing ulcer on a leg and a previous history of severe diarrhea with nocturnal incontinence of feces, and a case with partial foot-drop. The remainder were cases of typical diabetic neuritis with severe pain in one or more extremities, limitation of motion of the affected extremity and pain of such severity at night that, despite large doses of salicylates, barbiturates, codeine, etc., it interfered seriously with sleep. In all of the cases in addition to the routine clinical examination, with particular attention to the central nervous system, and the usual laboratory tests for diabetes (blood sugar, cholesterol, etc.) the examination, when indicated, also included the usual laboratory tests in such neurologic conditions-hemogram, gastric analysis, etc. For brevity the positive findings only will be given. With few exceptions the treatment consisted of daily intramuscular injections of 5 cc. of the extract. When Dr. Collens reported to the writer that the extract was not toxic in much larger doses, in a few cases the dose was 10 cc.

### DIABETIC CORD BLADDER

To exclude the possibility of a prostatic factor, the cases of "diabetic cord bladder" were restricted to females. In one (Case I) there had been incontinence of urine for over two months and in the other (Case II) for over two years. In both there had been such loss of sphincter control at night that, when the desire to urinate appeared, some urine had been invariably lost on the way to the bathroom. Also, in both cases before the incontinence of urine had developed there had been urgency for some time but, despite it, prolonged urination. In both also preceding the onset of the urinary signs, there had been marked numbness and tingling of the fingers or toes or both.

Case I. The first case (No. 5010/50) was that of a female, age sixty-eight, with diabetes

of sixteen years' duration, readily controllable with a diet consisting of approximately 250 gm. of carbohydrate, 45 gm. of fat, 110 gm. of protein and 20 units of unmodified insulin before breakfast and 15 units before the evening meal. On the day of her admission, November 16, 1950, to the Private Patient's Pavilion of The Montreal General Hospital the urine was free from sugar and acetone bodies, and the blood sugar was normal in the fasting state, namely, 0.117 per cent. The plasma cholesterol was 0.228 per cent. The gastric acidity curve showed complete achlorhydria.

In addition to the signs already mentioned, there were numbness, pain and stiffness in both arms and legs, more severe on the right side, for over three months, for which the patient had taken salicylates and codeine during the previous three weeks. There was also some numbness at the right angle of the mouth and general body ache. Her own description of the prolonged urination from the atony of the urinary bladder was "it comes like from a loose cork in a bottle." The relevant abnormal neurologic findings by one of our neurologists, Dr. Preston Robb, were diminished to absent ankle jerks and diminished vibration sense in both ankles and toes, especially on the right side.

As stated, the diabetes was under good control, but to exclude beneficial effects of good control as much as possible the diabetes was allowed to go out of control so that the urine throughout the period of investigation contained sugar but no acetone bodies, and the blood was persistently hyperglycemic; the blood sugars in the fasting state ranged between 0.188 and 0.250 per cent. Also, no steps were taken to correct the

achlorhydria.

The treatment consisted of intramuscular injection of 5 cc. of the extract daily. The day following the first injection the numbness had disappeared completely from the arms and legs. The general body aches had not decreased and there was still numbness at the angle of the mouth. After the third injection the urgency had decreased, there was no more incontinence of urine, the duration of the urination was shorter and, as the patient described it, it was "with more pressure." She had also slept for the first time in three weeks without any medication. After the fourth injection the pain and stiffness of the arms and legs had disappeared. After the sixth injection there was no urgency and no noticeable prolongation of urination. There was

slight recurrence of the numbness two to three times a day but the extract was discontinued. She was again seen by Dr. Preston Robb eleven days later and the neurologic report was essentially the same, with added comment about the improvement in the sphincter control.

Striking as this experience was, a possibility which had to be considered was coincidence, although no such experience with diabetic cord bladder had been met with previously by the writer in similarly severe cases. Beneficial effects of control of the diabetes and of the achlorhydria as contributing factors were excluded by the persistent hyperglycemia and glycosuria which were permitted and also, as stated, no attempt had been made to control the achlorhydria. That it was not a coincidence was suggested from the experiences in the second case in which the incontinence of urine was much more marked and of much longer duration.

Case II. In this patient (No. 441/51), a female age seventy, the frequency and prolonged urination and incontinence were of two years' duration, accompanied by marked paresthesias in the toes of both feet. In addition to the incontinence of urine at night there had also been incontinence during the day which necessitated wearing a pad constantly. The positive neurologic findings were absence of knee jerks on both sides and absence of vibration sense in both legs. Diabetic retinopathy was present. In this case also, to exclude beneficial effects from control of the diabetes as much as possible, the diabetes was allowed to go out of control with the result that the blood sugars in the fasting state ranged between 0.164 and 0.322 per cent. The average of all of the blood sugars in the fasting state was 0.237 per cent. The plasma cholesterol was 0.202 per cent.

The treatment here also consisted of intramuscular injection of 5 cc. of the extract daily. The first injection was given the day after the patient was admitted to the hospital (January 25, 1951). Three days later the paresthesias had disappeared almost completely. The following day incontinence of urine had also disappeared, but the urgency of urination was the same. After the seventeenth injection all urinary signs had disappeared. The extract was then discontinued. Four days later the paresthesias returned but disappeared after two more injections. The patient was discharged from the hospital on February 19, 1951; but because of the recurrence of the paresthesias after the extract had been

discontinued and as her husband was a physician, she was given sufficient of the extract for two injections a week for one month at home. To-date (June 25, 1951) there have been no recurrences of any of the signs.

Case III. This patient was a female (No. 3195/50), age fifty-eight, with diabetes of eleven years' duration, controllable with diet and 20 units of globin insulin once daily. Associated conditions were partial ulnar nerve palsy due to pressure with some atrophy of the interossei.

Following a cholecystectomy in July, 1950, this woman had developed a pressure palsy in the left hand; but other than the weakness and slight atrophy of the muscles and slight numbness of the fingers, there were no complaints. Two months later she began to complain of pain in the affected hand which had become increasingly severe, particularly at night, so that eventually codeine only gave some relief. The whole hand had also become so swollen that she was unable to flex the fingers. There was also some stiffness in both legs but the dominant complaint was the severe pain in the hand. During the last five days she had had very little sleep because of the severity of the pain, despite use of a barbiturate in addition to the codeine. The neurologic examination by Dr. Preston Robb showed a definite decrease in sensation over the area of the left hand supplied by the ulnar nerve, diminution of vibration sense in both legs, general diminution of the deep reflexes and complete absence of the left ankle jerk. "Diagnosis—ulnar nerve palsy due to pressure. Diabetic neuritis."

Daily intramuscular injections of 5 cc. of the extract were started on November 17, 1950. That night, for the first time in two months, she slept five hours without any medication. After the third injection the swelling of the hand had decreased. After nine injections there was still further reduction of the edema and still some pain, but it no longer interfered with sleep. On December 6, 1950, she was again seen by Dr. Preston Robb who reported: "There can be no question that subjectively she is better and that there is also objective improvement. I have the impression that she feels the tuning fork a little better in the ankles; the deep reflexes are the same; there is motor improvement in the hand and there is not the sharp line of sensory demarcation that there was before." On December 26, 1950, practically all of the edema had

disappeared; there was only slight impairment of flexion of the fingers, probably permanent, due to the atrophy of the interossei. The injections were reduced to twice a week and on January 11, 1951, after one week of complete freedom from pain, the treatment was discontinued.

In this case, also, it is to be noted that, as in Cases I and II, beneficial effects of control of the diabetes were excluded as a possible contributory factor in the recovery from the neuritis by having allowed persistent hyperglycemia and glycosuria until the extract had been discontinued.

Case IV. This patient (No. 4402/50), a male, age sixty-eight, had diabetes seven years which was readily controllable with diet and insulin.

The interests in this case, the first treated with the extract by the writer, were: (1) the diabetic neuropathies since the patient was first seen in 1945, including diarrhea and nocturnal incontinence of feces; (2) the advanced and generalized vascular degeneration with absent pulsations in the dorsalis pedis and posterior tibial arteries of both feet; (3) the non-healing ulcer on the internal malleolar region of the right foot; (4) the marked edema on the dorsum of both right and left feet and (5) the allergic rash from the extract, the only such experience to date.

For two months before this patient was admitted to the hospital (October 11, 1950) he had had such severe pain in the right leg that he had been unable to sleep for more than one hour at a time, despite large doses of salicylates, bromides, nembutal and codeine. Complicating the picture was some pain during the day during walking, which suggested pain from vascular occlusion rather than from diabetic neuritis.

As before his admission to the hospital, the urine was free from sugar throughout the time he was in the hospital and, with two exceptions, all of the blood sugars in the fasting state were perfectly normal. In the two exceptions the blood sugars were only 0.149 and 0.137 per cent. The gastric acidity curve was normal.

During the first week in the hospital while his general condition was being investigated, he had been unable to remain in bed except for short periods of time because of the pain. The need of bed rest for the healing of the ulcer on the leg was repeatedly pointed out to him, but he elected to walk about day and night because of the relief from the pain on walking. On October 18, 1950, he was given the first injection

of the extract and on the night of October 23rd -five days later—he slept six hours for the first time without medication since the onset of pain. After the ninth injection (October 24th) the pain had disappeared completely. He was then able to take the needed bed rest to hasten healing of the ulcer, during which an attempt was made to improve the blood supply to the ulcer area by physiotherapy. The daily injections of the extract were continued until November 2nd when the extract had to be discontinued because of the development of an allergic rash. There was, however, no recurrence of pain nor of paresthesias. When he was discharged from the hospital (November 6), the ulcer had practically healed. Since then he has been receiving Buerger's exercises and other physiotherapy measures to improve the circulation of the affected leg. His sleep has been normal since his discharge from the hospital. At times there is still a little pain in the calf of the leg during walking, which suggests pain from vascular occlusion rather than from diabetic neuritis.

As is well known, as bone destruction may be a trophic change from a diabetic neuropathy so may the latter cause marked edema of the affected extremity. The rapid healing of the ulcer and the disappearance of the edema on the dorsum of the foot, notwithstanding the little that has been accomplished in improving the blood supply to the leg, thus points to a neuritic rather than to a vascular factor in the previous non-healing of the ulcer and in the production of the edema. This may be assumed despite the general vascular degeneration in the body and, thus, the difficulty in such cases of determining the cause of the signs and symptoms.

Case v. This patient (No. 143/51), a male, age seventy-one had diabetes thirteen years, readily controllable with diet and insulin. Associated conditions were: generalized arteriosclerosis, hypertension, coronary thrombosis, heart failure, widespread osteo-arthritis and prostatic hypertrophy.

The interesting features in this case were: (1) the rapid relief from pain despite its long duration; (2) the severity of the neuritis as shown by the partial foot-drop; (3) the possibility of pain from osteo-arthritis and (4) the difficulty, at times in such cases, in differentiating between pain of angina pectoris and neuritic pain due to involvement of the nerves of the left chest wall.

During the last four years this man had been admitted to the hospital repeatedly for relief of

the constant pain, much more severe at night, in all four extremities with limitation of motion in both upper arms and pain also over the heart area. There was slight foot-drop of the left foot. The chief complaint was the pain which during the last two years had been so severe as to awaken him in the early hours of the morning and which was eased only by walking about. Large doses of salicylates to the point of salicylism, in addition to bromides, increasing amounts of different barbiturates and codeine at no time had given complete relief. During the day the most troublesome features were numbness and tingling, particularly of the fingers. For some time he had also complained of urgency of urination and, periodically, of incontinence of urine.

In this case, also, during his entire stay in the hospital (January 8 to January 19, 1951) in order to exclude possible beneficial effects of improvement of control of the diabetes, although this had been excluded repeatedly in previous studies, no attempt was made to control the diabetes, with the result that there was constant glycosuria but no acetonuria, and the blood sugars in the fasting state ranged between 0.178 and 0.217 per cent.

The fact that the most severe pain in the legs was experienced during the night and was relieved rather than aggravated by walking pointed to diabetic neuritis rather than to the osteo-arthritis as the dominant cause.

As there appeared to be no need for further investigation in view of the studies during the previous admissions, he was given his first injection of 5 cc. of the extract the day after admission. That night he was not given any medication and, as in the past, was awakened by the pain repeatedly. The following night, however, after the second injection, he slept throughout the night for the first time without medication—as he put it, "for the first time in four years," which may have been an exaggeration. The following night, however, he was again awakened because of the pain; but thereafter the improvement was progressive until the tenth injection when all of the neuritic manifestations had completely disappeared, including the partial foot-drop and the pain over the heart area. The incontinence of urine had also disappeared and the urgency of urination had lessened but, in view of the enlargement of the prostate and the vagaries of its signs, no significance is attached to the improvement of the urinary signs. To date there has been no recurrence of pain but there has been tingling of the fingers. In view, however, of its slightness he has not been given any more injections of the extract.

Case vi. A. B., a male, age fifty-eight, had diabetes thirteen years which was controllable without insulin whenever diet was followed carefully. Associated conditions were: obesity, cirrhosis of the liver (alcoholism), hypertension and coronary thrombosis.

Interesting features in this case were (1) the rapid recovery despite the progressive limitation of motion of both arms during a period of two months; (2) the almost constant hyperglycemia due to failure to follow treatment except occasionally; (3) the associated alcoholism and (4) the cardiovascular-renal degenerative changes, including the effects of alcoholism.

At his periodic office visit on December 18, 1950, he stated that he had had numbness and tingling of both hands daily during the past two months. Two weeks after the onset of the numbness and tingling he developed pain in both arms which had gradually spread to the shoulders and was particularly severe at night. This was followed by progressive limitation of motion of both arms so that during the last two weeks he had been unable to raise his arms to an angle greater than approximately 45 degrees. Physical examination confirmed this degree of limitation of motion. As usual, there was hyperglycemia but no sugar in the urine due to the raised renal threshold.

For a number of reasons it was not convenient for him to enter the hospital. He was, therefore, given an injection of 10 cc. of the extract in the office on that day. The following day he stated that he had slept well throughout the night for the first time since the onset of the pain and that the numbness and tingling had disappeared completely. He was given another injection of 10 cc. of the extract and the following morning, as he walked into the office he stated, "Look what I can do," and he raised both of his arms to a perfectly perpendicular position. The pain had disappeared completely. He was given another injection that day and one more the following day, but has had none since. To date not only has the pain not reappeared but there has been no return of the numbness and tingling although as usual there has been the same almost complete disregard of diet.

Case VII. J. T. S., a male, age seventy-five years, had diabetes seventeen years, readily

controllable with diet and 15 units of protamine zinc insulin once daily. An associated condition was incontinence of urine following prostatec-

tomy in April, 1949.

Other than the incontinence of urine since the prostatectomy this man had been well until the middle of October, 1950, when he began to notice numbness and tingling in both hands and some "stiffness" in both shoulder joints. About three weeks later this was followed by pain in both shoulders which had become increasingly severe, particularly at night. During the last two months he had been unable to sleep without medication because of the pain, and during the last four weeks had been unable to dress or feed himself properly. Like Case vi, he also found it very inconvenient to enter the hospital. Therefore, his daughter who is a nurse was given the necessary instructions for the intramuscular injections at home. He was given his first injection of 5 cc. of the extract on January 9, 1951. After the fifth injection the daughter reported "marked improvement." After the fifteenth injection he was completely free from all pain and all limitation of motion of both arms. To date there has been no recurrence of the pain, of the stiffness of the joints nor of the paresthesias in the hands.

The remainder of the cases do not warrant separate space for description of each. All were cases of typical diabetic neuritis, with numbness, tingling, formications, hyperesthesia and severe nocturnal pain in one or more extremities. In one, the patient cried most of the night because of the pain although she was practically entirely free from pain during the day. In all such cases, as is well known, no measures are of any avail unless the diabetes is under good control. Joslin<sup>3</sup> states he has never seen clinical improvement in diabetic neuropathy by any treatment regimen in the absence of effective diabetic control. In none of the cases, however, was an attempt made to control the diabetes in order to simplify the interpretation of the results with the extract alone. Despite this lack of control of the diabetes, in all, with the two previously mentioned exceptions, the relief from pain was complete. The number of injections which were necessary ranged between four and twenty-two.

As an example, there is the case of a woman, age seventy-one (No. 1155/51) who had been admitted for general investigation because of associated conditions and the difficulty of determining the extent to which the widespread

pain was due to diabetic neuritis and to what extent it was due to arthritis. As is well known, diabetic neuritis is not limited to the peripheral nerve but may involve the whole nervous system, central and autonomic. She was first seen by the writer in May, 1946, and when last seen in June 1950, the diabetes was regarded as moderately severe. Since then she had not consulted any physician and had practically completely ignored her diet. At her visit on February 28, 1951, the urine contained sugar but no acetone bodies, and the blood sugar was 0.357 per cent. The plasma cholesterol was 0.326 per cent and she gave the following history:

Early in December, 1950, she began to suffer from severe pain in the lower lumbar region and both hips and thighs and numbness and tingling in the toes of both feet. The pain had become constant and during the last three weeks she had been practically completely unable to do any of her house work. The nocturnal pain had become so severe that she had not been able to sleep "for more than a few minutes at a time." Also, because of the marked hypersensitivity of the skin she had found it difficult to tolerate not only bed covers but had also found it difficult to dress.

On March 13th, the day after her admission to the hospital, she was given the first injection of 5 cc. of the extract. That night for the first time in three weeks she slept five hours without interruption and with no medication. Since then she has been sleeping five to seven hours without any medication. On March 16th after the fourth injection she complained of "an occasional ache" only, and conditions have been the same since then.

### COMMENTS

As is well known, even in mild cases of diabetic neuritis complete recovery does not usually occur in less than weeks; in moderate cases it may be months; in severe cases it may be years and the neuropathies of the vascular and degenerative types are generally irreversible. The striking experiences, therefore, in the aforementioned group of cases have been the rapid recoveries even in those patients with marked vascular and degenerative disturbances. As stated, in the past no measure had been found effective for the relief of diabetic neuritis in the absence of effective diabetic control; whereas in these cases complete relief from pain and other signs were obtained despite the persistent hyper-

glycemia and glycosuria which were permitted in order to exclude control of the diabetes as a variable to consider in the interpretation of these results. The non-specificity of this extract is seen in its effectiveness in all of the types of cases, hyperglycemic, achlorhydria, neuritic, vascular and degenerative. Of interest here was the complete relief of the pain in Case v which was complicated by widespread osteo-arthritis, which fits in with Dr. Collens' experiences with this extract in osteo-arthritis in non-diabetics (personal communication).

Parenthetically, it may be noted that there was no evidence in any of the cases that this extract in any way had any effect upon the diabetes itself.

The chemical composition of the active constituent of this extract is as yet unknown. It is a clear, amber colored aqueous extract and, according to the studies to date made by Dr. Collens and his associates, is free from cortisone and ACTH. It contains trace quantities only of B<sub>12</sub> and folic acid, much less than are required to cause reticulocytosis. However, there is very little evidence that even large doses of the B-group of vitamins alter the course of a diabetic neuritis. With this Dr. Joslin is in complete agreement.<sup>3</sup> The extract appears to be non-toxic.

Since this paper was first prepared, as a preliminary report to Dr. Collens, no subsequent experiences have made it necessary to alter it in any manner. Sixteen other cases of diabetic neuritis of the extremities have been treated

since then with this extract under the same conditions of control and, in the total group, there have been to date (June 25, 1951) three failures only, an incidence of approximately 8 per cent.

In view of the neuropathic character of diabetic retinitis this extract was tried in two such cases (No. 4726/50 and 5162/50). In one (No. 4726/50) the ophthalmologist reported some reduction of the edema but, as far as vision was concerned, the treatment after thirty-five daily injections was a failure and therefore was discontinued. However, as the lesions in both cases were far advanced judging from the hemorrhages, little significance is to be attached to these findings. In the opinion of the writer, because of the satisfactory results with the different forms of diabetic neuropathies described, an extensive trial in the early stages of diabetic retinopathy is definitely indicated. Also worthy of investigation are the effects of prolonged use of this extract in cases of sexual impotency in diabetes.

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### The Problem of Cardiac Edema\*

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Y intention is to discuss somewhat philosophically the regulation of the fluids of the body in an effort to establish a background for the consideration of edema, particularly cardiac edema. In the argument I shall lean heavily on inference and analogy to the neglect of direct measurements, since direct measurements, although useful as a means of verifying or evaluating hypotheses, are too crude for the detection of the finer processes of biologic regulation. Biologic automatism, the tendency of biologic functions when disturbed to return to a state of rest or equilibrium, since it is an established principle, will be accepted, with the laws of thermodynamics, as points of reference.

So far as water is concerned, the essential functions which must be protected are the volume of fluid and its distribution in the various parts of the body. This involves the maintenance of (1) the total amount of water in the body, (2) the proper distribution of water between cells and extracellular fluid and (3) the volume of the circulating blood. The maintenance of these functions depends upon exchanges of water within the body and between the body and its environment. For regulation of the exchange of water with the environment, responsibility rests entirely upon the sense of thirst and the kidneys. So far as water is concerned, the gastrointestinal tract, sweat glands and respiratory system exercise not regulatory, but disturbing, influences. Their activities are linked not with the maintenance of the volume and composition of the internal environment but with provision of nourishment, regulation of temperature and regulation of gas exchange, respectively.

In spite of the indifference of the alimentary tract to the volume and composition of the body fluids, an animal, if free to follow its own dictates, drinks according to its requirements because the irresponsibility of the stomach and intestines is curbed by the sense of thirst. Volumes have been written about the failure of the kidneys to eliminate edema in various conditions but the continuation of thirst has aroused little curiosity. Nevertheless, in the formation and maintenance of edema it is an essential factor.

The volume that an animal will drink spontaneously at once is strangely proportioned to its needs. There must, therefore, be some mechanism for metering water connected with the sense of thirst which is activated by appropriate stimuli. The most potent stimulus to thirst appears to be the effective osmotic pressure of the extracellular fluid; that is, the sum of the partial osmotic pressures of those solutes that can not diffuse freely across cellular membranes, of which the most important ordinarily are sodium salts. Since these determine the distribution of water between cells and extracellular fluid, it may be the state of hydration of the cells that controls thirst. When the effective osmotic pressure (usually the concentration of sodium) in the extracellular fluid rises, drawing water from the cells and thereby dehydrating them, the animal becomes thirsty. 1-3 That effective osmotic pressure, not total osmotic pressure, is the stimulus to thirst is evidenced by the difference between the effects of sodium chloride and of urea. Compared with sodium chloride, urea, which diffuses through cells and extracellular fluids alike, provokes little thirst and that little seems to depend entirely upon its diuretic effect. 1 The anuric animal drinks only enough to maintain a constant effective osmotic pressure; that is, to keep the concentration of sodium in the serum from rising. It does not increase its drinking as the blood urea rises. The anuric animal has not been sufficiently considered by those who attribute edema to faulty action of the kidneys. The anuric animal does not become edematous unless it is given excessive amounts

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of water parenterally because it drinks only enough to keep the volume of fluid and the effective osmotic pressure of this fluid in the body normal. If, therefore, a subject develops edema with oliguria, the edema cannot be attributed to failure of the kidneys alone; some explanation must be found for the continued thirst.

When Darrow and Yannett<sup>4</sup> depleted animals of salt acutely, the animals, although they were dehydrated, evinced no immediate desire for water. They appeared to protect effective osmotic pressure at the expense of volume. Nevertheless, volume is not entirely neglected. Miners and stokers will, after profuse sweating, drink enough water to develop cramps and colic, signs of water intoxication referable to hypotonicity of the body fluids. Animals or men chronically depleted of salt will drink enough water to maintain the body fluids within reasonable limits even at the expense of persistent hypotonicity.<sup>5,6</sup>

The Starling<sup>7</sup> principle that exchange of fluid between the blood stream and the surrounding tissues is controlled by the balance between colloid osmotic pressure and hydrostatic pressure is an incontrovertible thermodynamic corollary of the established fact that extracellular fluid is an ultrafiltrate of plasma. In its application, however, the principle has been oversimplified. Transudation is controlled not by the oncotic pressure of the serum alone but by the effective oncotic pressure; that is, the difference between the oncotic pressure in the serum and that in the pericapillary fluid. Lymphedema, for example, in which protein accumulates because it is not removed by the lymphatics, is peculiarly intractable. The same condition obtains between ascitic fluid and serum in some patients with cirrhosis of the liver. Though proteins of the serum, and therefore the colloid osmotic pressure of the serum, in these states may not be greatly deficient, the effective oncotic pressure in the affected regions is extremely small. By the same token, it is not the capillary blood pressure but the difference between the capillary blood pressure and the tissue tension that counts. Finally, sufficient attention has not been given to the lymphatic system which serves as an auxiliary channel by which fluid may be returned to the circulation from the tissues.

Certain other implications of the Starling theory deserve more consideration than they have received. The oncotic pressure of the serum is essentially uniform throughout the circula-

tion. The concentration of protein in the serum in a particular region of the body can be measured with little error by analysis of blood taken from any part of the circulation. Capillary blood pressure, on the other hand, may vary widely in different parts of the circulation with vasomotor reactions or the force of gravity. The capillary pressure in a particular region cannot, therefore, be ascertained by measurements made in any other part of the circulation. The extent to which oncotic pressure can be increased is quite limited; but under the combined influence of vasomotor activity and the force of gravity capillary blood pressure can rise to a far greater degree. It is, therefore, possible for capillary pressure to compensate for any conceivable change of oncotic pressure, but the converse is not true; capillary blood pressure may and frequently does exceed the compensatory powers of oncotic pressure, in which case accumulation of fluid in the affected region is restrained only by tissue tension and lymph flow. This marks a distinction between edemas originating from hypoalbuminemia and those caused by venous

Since the membranes of all the cells in the body are freely permeable to water, the exchange of fluid between extracellular and intracellular compartments is controlled by the effective osmotic pressure of the extracellular fluid, which is usually synonymous with the concentration of sodium salts in this fluid. It follows that the state of hydration of the cells is independent of the volume of fluid in the body, depending only upon the concentration of sodium in the extracellular fluid. When sodium rises, the cells give up water and contract; when it falls, the cells take up water and swell. Sodium is, therefore, the instrument by which the distribution of water in the body is regulated.

Except insofar as the sense of thirst protects it, the integrity of the internal environment depends upon the kidneys, which have a regulatory or conservative function that is at least as important as their excretory function. For the most part, waste products are excreted by filtration with or without secretion or back-diffusion, but without active reabsorption. Their excretion, which requires a certain amount of water therefore, depends upon their concentrations and the rate of filtration. Since their concentrations in the serum are determined by the rate of metabolism, which bears no relation to the supplies of water in the body, these solutes

preempt water for their excretion irrespective of the state of hydration of the animal. Sodium salts, on the other hand, can be reabsorbed to any extent from the renal tubules by active processes. That fraction of the filtered sodium salts which is not reabsorbed, like the waste products that are not reabsorbed, limits the reabsorption of water; but, insofar as it is not restricted by the demands of these solutes, water can also be actively reabsorbed from the tubules. Conservation of water by the kidneys can, therefore, be achieved (1) by maximum reabsorption of water and (2) by maximum reabsorption of sodium salts which permits further reabsorption of water.

It is through the reabsorption of water and salt that the automatic simultaneous regulation of the effective osmotic pressure and the volume of the fluids in the body is achieved. If tubular reabsorption of water and sodium salts is regulated in accordance with the volume and effective osmotic pressure of the body fluids, by humoral agents, automaticity with respect to both functions could be most simply and efficiently attained if the two functions were reciprocally related; that is, if reabsorption of water was governed by effective osmotic pressure and reabsorption of salt by the volume of the body fluids. So far as water is concerned such a relation was demonstrated by Verney and O'Connor.8,9 Infusion of hypertonic salt solution into the carotid arteries of animals provoked antidiuretic activity while solutions of urea of equiosmolar concentration did not. It has been shown by a variety of other methods that extracts of the posterior pituitary gland control the terminal reabsorption of water from the renal tubules and that the posterior pituitary gland behaves as if its activity were controlled by the effective osmotic pressure of the serum or the state of hydration of the cells, which is governed by the effective osmotic pressure of the serum and extracellular fluids.

The agent that governs the reabsorption of sodium chloride and the stimulus by which it is activated cannot be so precisely defined. There are strong reasons for identifying the agent with the adrenal cortical hormone—or perhaps with an adrenal hormone—and the stimulus with the volume of fluid in the body. As yet it has been impossible to demonstrate that any adrenal steroid or even ACTH consistently behaves as such a salt-retaining hormone should. It may be, however, that the action of the adrenal hor-

mone, like that of the posterior pituitary antidiuretic hormone, is conditioned. Welt, Seldin and Cort10 have found that not only ACTH but also DOCA appear to have no action on the excretion of salt, water or potassium if the individual or animal to whom they are given is receiving minimal amounts of salt. The quality of volume or its mode of expressing itself is peculiarly illusory. Effective osmotic pressure is easily measurable and is essentially uniform throughout the body. An osmometer placed at random anywhere in the body would give essentially the same results. On the other hand, an increase of volume may involve only one compartment or one region of the body. The cells could not serve as volumeters, since the volume of the cells is correlated not with the amount of fluid in the body but with the effective osmotic pressure in this fluid. The kidneys appear to be indifferent to the volume of the extracellular fluid outside of the circulatory system. Transudation of fluid into a thrombophlebitic leg or the subcutaneous tissues of a nephrotic patient leads to retention, not excretion, of salt and water. The circulating blood stream seems best qualified to serve as a volumeter or receptor. But even this is an intangible function because of the variable distribution of blood in the vascular system. If the blood becomes pooled in one region, the quantity of blood in other parts of the circulation may be deficient even when the total volume of blood in the vascular bed is expanded. The adrenal cortex, kidney or any other organ would develop something like acute schizophrenia trying to respond to the impulses that might come to them under these circumstances. Metering of volume must be a function of some particular part of the circulation or of some particular property of the blood.

It is, of course, not only possible but probable that the regulation of reabsorptive processes is not entrusted solely to the posterior pituitary and adrenocortical hormones. Acid-base and osmotic equilibria are not altogether independent. Activity of the nervous system may not express itself entirely through vasomotor control of glomerular filtration. Effective osmotic pressure and fluid volume and their control can, however, be considered without preconceptions concerning the agencies through which this control is exercised.

Edema can be defined as an expansion of the volume of the extravascular portion of the extracellular fluid. An increase of blood volume

alone would not be edema but plethora or hemodilution. Expansion of the intracellular fluid would be merely a consequence of reduction of the effective osmotic pressure of the extracellular fluid. The term edema requires some quantitative qualification. The transitory expansion of the extracellular fluid that follows the drinking of a liter of water would not merit the term edema, nor would the transfer of water from the intracellular to the extracellular compartment in response to the ingestion of salt or injection of hypertonic salt solution. If, however, there is agreement with respect to the qualitative definition, considerable differences concerning the quantitative limitations will be of no great moment to this argument.

If the definition is accepted, the formation of edema must involve two components: (1) increase of the total amount of water in the body and (2) displacement of this fluid into the extravascular space. Since Cohnheim's 12 classic experiments the injection of even massive amounts of fluid has failed to produce obvious puddling in the subcutaneous tissues or serous cavities, whereas it is relatively simple by a variety of methods to produce such puddling by procedures that enhance the escape of fluid from the blood stream. Furthermore, even the puny success that has attended the efforts to induce edema by plethora of fluids has been attained only by the forcible injection of these fluids, while the edema that follows transudative processes requires no more than freedom to satisfy the sense of thirst. Retention of salt provokes retention of water because accumulation of sodium in the body activates the antidiuretic hormone; but if the circulatory system is intact, the retention does not reach proportions of edema so long as the subject has free access to water. So long as the circulation is intact, DOCA causes diabetes insipidus, not edema<sup>13,14</sup>—the latter occurs only if fluid is displaced from the vascular bed owing to circulatory failure. The slight accumulation of fluid that occurs must be attributed to thirst, incited by its natural stimulus. Retention of water should have no comparable effect because it abolishes thirst. In the initiation of edema, salt should have a greater influence than water because its reabsorption is less restrained. Reabsorption of water is limited by other solutes in the urine and such salt as escapes reabsorption. But salt would not produce edema in a free animal if it did not provoke the animal to drink.

The sequence of events in the development of hypoalbuminemic edema can be outlined in the following manner. If serum albumin falls, an excessive amount of fluid escapes from the circulation, the volume of which consequently diminishes. This activates the reabsorption of sodium chloride. As the concentration of sodium in the serum rises it, in return, elicits antidiuretic activity. The process can be rapidly reversed by injection of serum albumin or some other colloid that restores the oncotic pressure of the serum, thereby restoring the blood volume and reducing transudation.

The priority of salt in the production and maintenance of the edema can be demonstrated in various ways: (1) If the intake of salt is extremely limited, edema will diminish and equilibrium will be established in the exchanges of both salt and water. Large amounts of water can be given without appreciably increasing the edema, but the excretion of sodium salts will remain minimal. (2) If salt is given, it will be retained and edema will increase immediately. (3) Injection of salt-poor human serum albumin induces excretion of sodium chloride in equivalent amounts. Although the action of the injected albumin on the oncotic pressure of the serum is transitory, edema reaccumulates only gradually in proportion to the quantity of sodium that is retained. Its accumulation is not appreciably accelerated by ingestion of water. (4) Mercurials, which inhibit the reabsorption of sodium, may provoke similar diuresis, although they do not rectify the dislocation of fluid that is responsible for the edema.

This priority of salt is not, however, absolute; the serum sodium of the nephrotic patient is seldom elevated. This in itself is not surprising since primary retention of sodium provokes thirst. This does not explain the fact that in the nephrotic syndrome serum sodium tends to be low. Welt and Orloff<sup>15</sup> found that injection of albumin first increased the excretion of water. Only after serum sodium had risen as a result of the loss of water did the excretion of sodium increase. Luetscher and Deming<sup>16</sup> have made a similar observation. Despite the priority of sodium, therefore, and its predominance in the control of edema, a certain amount of water seems to be retained in excess of sodium. This phenomenon, which is encountered in an exaggerated form in other conditions, implies that the ingestion of water is not controlled entirely by the effective osmotic pressure of the

serum and that an additional increment is taken and retained in behalf of some other function. It is reminiscent of the unsatisfying thirst of the salt-depleted subject with depleted fluids. It suggests a reaction to diminished volume.

into the lower extremities. Although glomerular filtration presumably fell, judging from the urea excretion, this cannot be held responsible for the salt retention which continued after urea excretion had returned to normal. The experiment can be so arranged that glomerular

Table I
EFFECT OF STATIONARY STANDING ON VOLUME AND COMPOSITION OF URINE

	Minutes					
		Volume (cc./hr.)	Urea (mM/hr.)	Na (mEq./hr.)	K (mEq./hr.)	Serum* Volume %
Up and about	143	23.1	9.7	2.48	2.31	100
Standing still	127	10.4	3.6	0.21	1.79	89
Supine (1)	67	26.0	12.5	0.68	2.62	-0
(2)	107	22.3	23.6	2.05	3.37	115

<sup>\*</sup> Calculated from formula,

 $\frac{\text{Plasma volume}_1}{\text{Plasma volume}_2} = \frac{(1\text{-relative cell volume}_2) \text{ hemoglobin}_1}{(1\text{-relative cell volume}_1) \text{ hemoglobin}_2}$ 

The sequence of events that follows venous stasis differs from that produced by hypoalbuminemia in only one respect: the transudation responsible for the initial reduction of blood volume originates from an increase of capillary blood pressure instead of a reduction of oncotic pressure. The subsequent consequences are the same. In Table 1 are data from experiments of Goodyer and Seldin.<sup>17</sup> The subject, a normal male who had received no meals and limited amounts of water for twenty-four hours, after walking about for two hours and twenty-three minutes assumed the stationary standing position. His urine volume promptly fell to about one-half, urea excretion to one-third and potassium excretion to one-fifth their former values; but the excretion of sodium fell to onetenth its previous value; in fact, in the two hours of stationary standing the urine contained less than 1 mEq. of sodium. In the next hours in the recumbent position, urine volume, urea and potassium promptly returned to normal; but sodium in the urine remained low for a longer period. During stationary standing plasma volume diminished by 11 per cent; in the recumbent position it rose 15 per cent. Without any significant change of the total volume of fluid in the body, excretion of sodium and chloride almost ceased in association with a displacement of blood and transudation of fluid

filtration does not change significantly. Harrison and associates<sup>18</sup> have demonstrated that the mere change from the recumbent to the sitting position diminishes the excretion of salt. The reaction comes on so promptly that it must precede transudation although its reversal is delayed until blood volume is reconstituted. At first the blood in the upper part of the body diminishes merely because an unusual amount is pooled in the lower extremities. Later, owing to the increased hydrostatic pressure in the capillaries of the lower extremities, fluid escapes from the circulation. The sequence of events in both hypoalbuminemia and venous stasis is consistent with the hypothesis that reabsorption of salt is regulated in accordance with the volume of the circulating blood or some function of the volume of the circulating blood. In hypoalbuminemia the tendency to transudation is general because it arises from a deficiency that affects the circulating blood as a whole; but it can be accelerated by the force of gravity. The oliguria of stationary standing comes on so rapidly as to suggest that it may be initiated by the displacement of blood in the circulation. To accelerate reabsorption of sodium it may not be necessary to reduce the absolute volume of the circulating blood but merely to divert it from some particular region in which the volumeters or receptors are located. This may be the head.

Harrison and associates<sup>18</sup> have shown that application of a cuff to the neck with sufficient pressure to cause venous congestion in the head accelerates the excretion of sodium.

Although the effects of serum albumin in hypoalbuminemic edema are spectacular, the results of expanding the blood volume of normal subjects by means of serum albumin have been inconsistent. Welt and Orloff<sup>15</sup> found that injection of 25 per cent albumin solution diminished the excretion of both water and sodium chloride, especially the latter. When the same quantity of albumin was injected as a 4 per cent solution, in either glucose or saline, it accelerated the elimination of water while excretion of salt was unaffected. Both solutions expanded the volume of the circulating blood; but the 25 per cent solution raised oncotic pressure whereas the 4 per cent solution did not. It is conceivable that there are two criteria of blood volume: (1) hydrostatic pressure and (2) hemoconcentration. If oncotic pressure was the index of hemoconcentration, these experiments with albumin would be explicable. The 4 per cent albumin solution increased volume only, thereby exerting only a hydrostatic effect which would be diuretic. The 25 per cent solution increased oncotic pressure, indicating hemoconcentration, thereby evoking an antidiuretic reaction. In the hypoalbuminemic state hemoconcentration would never become evident because oncotic pressure is always subnormal. In fact, the effects of excessive oncotic pressure or any other index of hemoconcentration would be detectable and useful only when, as in the normal subject, the blood volume was normal or expanded. When it was contracted, hydrostatic pressure would exert its own antidiuretic effect. This is speculation, but speculation consistent with observation, and therefore a path for inquiry.

In the ascites of cirrhosis of the liver the effective oncotic pressure in the region of transudation is greatly reduced because the concentration of protein in the transudate is high. At the same time the portal venous pressure, and presumably the capillary pressure, is greatly increased. There is, then, a large hydrostatic force promoting transudation with an unusually low opposing oncotic force. Attempts to increase the oncotic force by injections of albumin are defeated by reason of the fact that the concentration of protein in the ascitic fluid rises pari passu with that of the serum. <sup>19</sup> If dependent edema accompanies ascites, this may respond

to injections of albumin, at least while the legs are not dependent, unless there is associated heart failure, when digitalis may be effective. The ascitic fluid is effectively segregated or trapped by the unopposed hydrostatic pressure. As proof of this trapping, if a communication is made between the ascitic cavity and the subcutaneous tissues of the abdominal wall by means of a plastic tube, ascites will be mitigated or relieved. 20,21 The fluid escapes into a region where the protein can be removed by the lymphatics and where the capillary pressure is not unduly high. So long as these conditions prevail ascites will remain in abevance. Unfortunately, such relief is short-lived because a new impermeable sac is formed in the subcutaneous tissues which acts merely as an extension of the peritoneal cavity.

Ascites may diminish or reaccumulate less rapidly after paracentesis if the patient is given a diet containing minimal quantities of salt. Under these circumstances, as in hypoalbuminemic edema, ascites may remain stationary or increase only gradually in proportion to the sodium that is retained. Extra water may be excreted quantitatively, albeit with some delay; but administration of salt causes a rapid accession of ascitic fluid. Mercurial diuretics may delay the accumulation of ascites or even promote its absorption. Salt therefore appears to have a priority in the production of the ascites. Nevertheless, the concentration of sodium in the serum is usually slightly depressed, rising with improvement and spontaneous diuresis. 22 There is a tendency to retain water in excess of salt.

After a large paracentesis if an infusion of glucose is given, little of the injected fluid is excreted. Ascites reaccumulates and the concentration of sodium in the serum may fall so low that the patient goes into collapse and coma. Although these symptoms can be rapidly relieved by an infusion of hypertonic sodium chloride, this ultimately leads to the speedier recurrence of ascites. It is not necessary to inject fluid to evoke these dramatic reactions. Patients, if unrestrained, will frequently drink enough water after paracentesis to produce hyponatremia. After a large paracentesis which may remove 900 mEq. of sodium or more from the body, owing to the reduction of abdominal pressure without comparable change of portal capillary pressure, fluid is immediately poured into the peritoneal cavity causing hemoconcentration.23 There is a rapid enough reduction of the volume of the circulating blood to divert it from any volumeter. Not only is the excretion of water and salt reduced but thirst is provoked. It may be significant that if immediately after paracentesis an intravenous injection of albumin is given, hemoconcentration is less striking, ascites reaccumulates less rapidly and thirst and the decline of serum sodium are mitigated.

Ascites illustrates the priority of salt in the production of transudation, together with the tendency to accumulate water in excess of salt. It is a prime example of the precedence of transudation over reabsorption of salt and water in the production of edema. Finally, it represents a condition in which both thirst and renal reabsorption of water seem to be activated not by effective osmotic pressure but by some other stimulus. The phenomena that have been described suggest that this is the volume of the circulating blood or the function that acts upon the volumeter.

Stationary standing involves diversion of blood from the general circulation into a localized pool and transudation of fluid under the influence of hydrostatic pressure. Epstein, Goodyer, Lawrason and Relman<sup>24</sup> have shown that injections of albumin, even in isooncotic concentrations, do not reverse the antidiuretic effect of this position. The person with a thrombophlebitic edema must experience daily in an exaggerated degree the phenomena of stationary standing. Such a person probably does not spend the day with the circulating blood and extracellular fluid of the rest of the body depleted by its diversion to the legs. Presumably lack of salt would not inhibit drinking entirely; therefore, thirst would have to originate from some other source. Franklin Epstein has informed me from personal experience that stationary standing engenders thirst. In addition, Nelson and Welt25 have found that stationary standing subjects do not excrete an additional load of water.

All this evidence suggests that when blood is diverted from certain parts of the circulation or when fluid escapes from the circulation under conditions that preclude its return, both salt and water are reabsorbed. Thirst continues and reabsorption of water does not cease when there is an excess of water over salt with consequent reduction of the effective osmotic pressure of the body fluids. This is similar to the state of the subject with primary salt depletion attended by circulatory deficiency and hemoconcentration.

These phenomena of trapped edema are consistent with the hypothesis that the regulatory force to which the salt-retaining hormone reacts is the volume of the circulating blood, the fullness of the blood stream or some function usually related to the fullness of the blood stream wherever this may be registered. That the effective osmotic pressure of the serum or the state of hydration of the cells is a regulator of the antidiuretic hormone of the posterior pituitary appears to be even better established, because inferential evidence is supported by the direct experiments of Verney and O'Connor. 8,9 Nevertheless, volume is not sacrificed completely to effective osmotic pressure and, therefore, must also be defended by reabsorption of water. This defense would be needed when both volume and effective osmotic pressure are reduced. Under these circumstances reduction of effective osmotic pressure would inhibit antidiuretic activity when, in behalf of volume, it should be stimulated. It is difficult to conceive a mechanism by which the posterior pituitary gland or its intermediate receptors could differentially evaluate two such contradictory functions. It may be necessary to postulate two agents that govern thirst and reabsorption of water. The effect of all true antidiuretic agents must be conditional upon the prior reabsorption of salt, because sodium that remains in the tubules limits the reabsorption of water.

If the postulated agent, like the posterior pituitary antidiuretic hormone, promoted reabsorption of water and the actions of the two were stimulated by diminution of volume and increase of effective osmotic pressure, respectively, there would be no conflict between them in the adjustment of these functions. The volumereceptor might be situated in the head and be activated by hydrostatic pressure. This would explain the antidiuretic effect of the erect posture and the diuretic effect of compression of the neck. Reabsorption of sodium might be promoted by this same hydrostatic factor and by some indicator of hemoconcentration as well. This latter might be, as Welt and Orloff<sup>15</sup> have suggested, the oncotic pressure of the serum. Antidiuresis appears to be regularly linked with thirst.

There is every reason to believe that cardiac edema is governed by the forces that control the exchanges and disposition of fluid in other conditions. It is more profitable, therefore, to consider it in comparison with analogous states than to set it apart from other edemas with special cardiologic ground rules to govern its behavior. The conventional sequence of events in the development of cardiac edema, presented in the left hand column of Table II, differs from the sequence of hypoalbuminemic edema in

#### TABLE II ORMATION OF CARDIAC EDEMA

FORMATION OF	CARDIAC EDEMA
1. Starling	2. Forward Failure
Increased venous pressure	Retention of salt and water
Increased capillary pres- sure	Expansion of plasma vol- ume
Transudation	Increase of venous and
Reduction of plasma vol- ume	capillary blood pressure

Retention of salt and water Transudation

only one respect: the initial displacement of fluid from the blood stream is attributed to excessive capillary blood pressure instead of deficient colloid osmotic pressure. In both conditions retention of salt and water by the kidneys is a natural consequence of this dislocation of fluid. It has been contended that this sequence is not consistent with the facts, that retention of salt and water precedes the increase of venous pressure and that the volume of the circulating plasma is not contracted but expanded. The sequence of events shown in the right hand column, to which the term forward failure has been attached, has therefore been proposed.26 The Starling sequence has in its favor that it conforms to the laws of thermodynamics and to the physiologic principles that govern exchanges of water in the body and between the body and its environment. It also brings cardiac edema into the general family of edemas instead of leaving it an orphan.

There is nothing in the known phenomena of congestive failure to provoke the primary retention of salt and water if the factors that promote salt-retaining and antidiuretic activity have been correctly identified. It has, therefore, been necessary to hypothesize a disturbance of renal blood flow or glomerular filtration, or both. Variable degrees of reduction of renal plasma flow and glomerular filtration, especially the former, have been demonstrated by numerous observers in various proportions of patients with congestive failure.27-29 Even those who might contest the statement that reduction of glomerular filtration does not necessarily diminish the excretion of salt and water could not contend that diminished renal plasma flow with normal glomerular filtration would have any such effect.

In any case, however, this question can not be settled on a statistical basis. Since glomerular filtration has not been invariably reduced in any series of patients, such reduction is not essential to the production of edema. In a series of twelve patients with congestive heart failure Earle and associates<sup>30</sup> found that four responded to intravenous digoxin with prompt acceleration of the excretion of sodium and water, while renal plasma flow and glomerular filtration did not change. In the remaining eight these functions did increase slightly or moderately; but in general these increases were relatively smaller and occurred later than the diuresis. In one patient with an initial serum sodium of only 113 mEq. per L., excretion of water, potassium and chloride, but not sodium, increased with the same celerity far in advance of renal plasma flow and glomerular filtration. Whether or not reduction of glomerular filtration contributes to the retention of salt and water, tubular reabsorption is chiefly responsible.29-31 The case with low sodium exemplifies (1) the tendency already mentioned for water to be retained in excess of sodium under certain circumstances and (2) the delivery of water before sodium in such cases.

The prior position of retention of salt and water, especially the former, is not confined to heart failure; it is just as evident in hypoal-buminemia, stationary standing and cirrhosis of the liver. It was mentioned that postural transudation provokes the sensation of thirst and that, if an extra load of water is given, it will not be excreted in the usual manner. Therefore, although the most conspicuous initial event in stationary standing is accelerated reabsorption of salt, the subject evinces the reactions that have been described as characteristic of deficient volume, in spite of the fact that there is no true deficiency but merely a dislocation of the volume of the circulating blood.

If blood volume is necessarily increased in congestive failure, which in my opinion is not incontrovertibly established although it can not be categorically denied, the problem remains why this disturbance, which ordinarily promotes excretion of salt, should, in heart failure, accelerate its reabsorption. The increase must be of such a kind that the volumeters which ordinarily inhibit reabsorption of sodium are not apprised of the fact. It is conceivable that the increment of blood is segregated in the congested liver or in the extremities, regions of

the blood stream to which the kidneys are insensitive, while the regions which contain the volume-receptors to which the kidneys respond

are relatively empty.

The theory of "forward failure" postulates not only that the blood volume increases but that this increase induces transudation. Since transudation is governed by the Starling equilibrium, this requires that at least in those regions in which edema collects either the effective oncotic pressure be reduced or the capillary pressure be increased. Moderate deficiency of serum albumin is so common as to be almost the rule in heart failure. Although it must contribute to the formation of edema, it is usually not sufficient to be the chief cause of edema. If it were, injections of serum albumin should have a striking diuretic effect which they usually do not. Transudation in heart failure must therefore be attributed to an increase of capillary blood pressure which presumably arises from venous congestion. An increase of capillary pressure is as necessary for the formation of edema in "forward failure" as it is in the Starling sequence. Whatever may be the precise sequence of events in congestive failure, most observers agree that the commonest circulatory disorders in this condition are reduced cardiac output and increased venous pressure. 28,32-36 In Earle's<sup>30</sup> experiments with digoxin, venous pressure changed first, excretion of salt and water increasing synchronously with this change. Even if the venous pressure was not above normal limits, it fell distinctly with diuresis, but so rapidly that the drop could not have been a result of the diuresis. All things are relative; circumstances alter cases. Even if the edema of heart failure is due to increased venous pressure, exact correlation between the presence and degree of edema and the elevation of venous pressure cannot be expected unless all other factors that influence transudation remain constant. The edema of a nephrotic patient increases with assumption of the erect position. In such a patient a given venous pressure will provoke greater regional transudation than it will in a subject with a normal serum oncotic pressure. Although the serum albumin in heart failure is seldom low enough of itself to induce appreciable edema, any reduction must contribute to the transudative process. As hypoalbuminemia increases, the venous pressure required to produce edema must diminish. Hypoalbuminemia is only one of the factors that

can modify the effects of venous pressure. Anemia is another. It is not surprising, then, that edema should appear with various venous pressures; it is significant that its disappearance should consistently coincide with a fall of venous pressure. Earle measured venous pressure in the right auricle or the femoral vein; pressures in regions of transudation were presumably greater. Effects of posture or any other factors that promote transudation are exaggerated in congestive failure. It must have occurred to all of you that the orthopnea of heart failure is an obstacle to diuresis. I suspect that it would decrease the tolerance to a cuff about the neck.

It has been suggested that venous congestion of the kidneys may be responsible for the oliguria of heart failure. It seems unlikely that this is an important factor in most cases. It has been recognized since the time of Heidenhain that moderate venous congestion, by increasing capillary pressure, produces diuresis. With the exception of Hall and Selkurt<sup>37</sup> observers are generally in agreement that only when renal pressure rises to considerable heights does it reduce excretion. <sup>38,39</sup>

With respect to the priority of salt, cardiac edema does not differ essentially from other types of edema. Actually, a good argument for the priority of water could be drawn up because cardiac edema resembles cirrhotic ascites in the fact that water may be—perhaps generally is retained in excess of salt. In the clinic, hyponatremia is encountered more frequently than hypernatremia in heart failure but it is impossible to determine how far this is an inherent characteristic of the condition or the result of therapy, especially the use of mercurial diuretics. Mercurials specifically inhibit tubular reabsorption of sodium chloride. Patients with congestive failure may after mercurial diuresis, although still edematous, like patients with cirrhosis develop such severe sodium deficits that they suffer circulatory collapse. Like the cirrhotic patients they respond favorably, so far as the circulatory status is concerned, to hypertonic salt solution; but this seldom provokes diuresis tending rather to promote the reaccumulation of edema. Some reason must be found for the fact that the cardiac patient will drink enough water to cause hyponatremia. The formation of edema requires more than failure to excrete water. The anuric patient does not develop edema if left to follow his own instincts. He will drink only enough water to

replace that lost through extrarenal channels. The natural stimuli to thirst are elevation of the effective osmotic pressure of the body fluids and reduction of the volume of the blood or that function which activates the volumeter, the same function that promotes reabsorption of water by the renal tubules. The first of these factors, effective osmotic pressure, will be active only so long as serum sodium is above normal. If, then, the cardiac patient will drink enough water to produce hyponatremia, it may be inferred that the impulse to drink must arise from the fact that the volumeter registers a deficiency of fluid.

Increased venous pressure, even when measured by conventional methods or in the right auricle, is one of the commonest if not the most common circulatory disorder of heart failure. If it were measured in the regions of transudation, its frequency and magnitude would undoubtedly prove to be greater. The phenomena encountered in cardiac edema, including salt retention, are those which regularly attend increase of venous pressure. There is no evidence that they can be produced by circulatory disturbances of the kidney or reduction of glomerular filtration. If the volume of the circulating blood is increased, some place must be found for the increment since fluid is incompressible. Some may be pooled in the liver, some in the peripheral circulation. The kidneys behave as if it were not in the regions in which expansion of the circulating blood ordinarily accelerates excretion of sodium. It must, however, be so distributed that it increases capillary pressure in the regions where transudation occurs. That increased blood volume is not essential for this transudation is attested by the sharp reduction of urine flow that is precipitated by pulmonary edema which is accompanied by hemoconcentration. Vigorous use of diuretics sometimes has a similar effect. The kidneys do their part in excreting fluid brought to them by the blood; but because the edema is effectually trapped, the fluid withdrawn from the circulation cannot be replaced. The transudation of cardiac edema and the reactions it induces have the characteristics encountered in conditions in which fluid is trapped or segregated outside of the blood stream by unbalanced hydrostatic pressure at the expense of the volume of the circulating blood or in such a manner that the circulating blood is diverted from the volumeters. The most significant of these reactions are the continued reabsorption of water by the renal tubules and the persistence of thirst when the concentration of sodium in the serum is depressed.

From these considerations comes the conviction that the logic of the conventional theory of the formation of cardiac edema with its sequence firmly based on Starling's principles cannot be lightly set aside. If undue emphasis seems to have been laid upon refutation of the theory of "forward failure," it is only because this is a convenient foil, being so diametrically opposed to the conventional sequence. But, irrespective of these theories, I am convinced that the problem of cardiac edema cannot be properly considered without reference to the physiologic principles that govern water metabolism and the control of exchanges of water and salt in normal subjects and the forces responsible for the production of transudation and edema in analogous states.

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# Seminars on Congenital Heart Disease

## Congenital Heart Disease\*

An Introduction and Classification

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THE last fifteen years have seen a rapid and progressive interest in congenital heart disease. This is primarily the result of advances in the surgical treatment of congenital malformations of the heart and great vessels. Gross published his first report on the ligation of patent ductus arteriosus in 1939.1 The first operation for coarctation of the aorta was performed by Crafoord in Sweden in 1944,2 and by Gross in this country in 1945.3 Blalock performed the first operation for tetralogy of Fallot in 1944.4 Before that time interest in congenital heart disease was mainly academic and centered on purely pathologic aspects of malformations of the heart. This pre-surgical period is climaxed by the work of Maude Abbott who forty years ago gave to the medical world the first comprehensive analysis of congenital heart disease.5 Maude Abbott probably foresaw the developments in surgical treatment of cardiovascular defects. For instance, she mentioned the work of Munro who suggested ligation of a patent ductus arteriosus in 1924,6 and she also mentioned the work of Carrel and Tuffier, who attempted to enlarge the pulmonary ostium in pulmonic stenosis by incising the stenotic valve and patching the wall of the stenosed vessel from without.

The rapid advance of surgery of the heart and great vessels in congenital heart disease has made an understanding of congenital heart disease of general importance. Therefore, it has become advisable that the internist and the pediatrician cooperate with the surgeon in the evaluation of patients with congenital heart disease in order that operable cases may be selected and benefited by surgery. The important developments which have made this possible have taken place in the field of clinical medicine, applied physi-

ology and radiology. It is the purpose of this present review to present only an introduction to this field. For more detailed information, the reader is referred to subsequent articles of this series or to previous reviews of this field.<sup>7–15</sup>

ADVANCES IN THE FIELD OF CLINICAL MEDICINE

Careful evaluation, inspection and physical examination of the patient may throw considerable light on diagnosis in congenital heart disease. A history of attacks of pneumonia in patients with congenital heart disease may be indicative of increased pulmonary blood flow or increased pressure in the pulmonary arterial tree. A study of the growth and development furnishes information on the severity of the cardiac lesion. The time of onset of cyanosis, the degree of dyspnea and of exercise tolerance, the habit of squatting, a history of loss of consciousness and of cerebral vascular accidents are all of aid in assessing the severity of the malformation and in arriving at a diagnosis and a form of therapy.

Inspection of the patient is of importance. Cyanosis and clubbing are always strongly suggestive of congenital malformations of the heart, particularly if the history reveals that these signs were present in early youth. The presence of cyanosis in the lower extremities alone suggests an infantile coarctation or interruption of the aortic isthmus with a patent ductus arteriosus, or a patent ductus arteriosus with reversed flow due to increased pulmonary resistance.

Thorough physical examination is essential. Evidence of a high pulse pressure with a femoral

shock is characteristic of a patent ductus arteriosus. The pathognomonic finding in coarctation of the aorta is high blood pressure in the upper extremity and low blood pressure in the legs.

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The presence of a large heart and of severe cyanosis suggest transposition of the great vessels. <sup>15</sup> A small heart, on the other hand, may be indicative of an operable malformation, usually the tetralogy of Fallot. A study of the murmurs over the heart and chest may be of the utmost

NORMAL 20000 FEET 140 120 100 80 60 40. 20 0 160 CONGENITAL HEART DISEASE 140 120 100 80 60 40 20 **00078** AIR INSP. ALV. ART. OXYGEN PRESSURE GRADIENTS

Fig. 1. Gradients in oxygen transfer system from inspired air to capillary blood in normal individuals at sea level and at high altitude, and in patients with congenital heart disease of the cyanotic type. (Courtesy of the *Bull. Johns Hopkins Hosp.*, vol. 83, no. 5, 1948, Johns Hopkins Press, Baltimore, Md.)

value or may be extremely confusing. As a rule the murmurs in congenital heart disease are not of as great diagnostic importance as they are in acquired heart disease.

An enlarged liver in the absence of cardiac failure suggests the presence of an abnormality of the tricuspid valve. An enlarged pulsating liver indicates the presence of tricuspid atresia or of pulmonic stenosis with a small auricular septal defect.

## ADVANCES IN THE FIELD OF ROENTGENOGRAPHY AND FLUOROSCOPY

Fluoroscopy and x-ray examinations are particularly useful in the diagnosis of congenital heart disease. Fluoroscopy permits an estimation of the size and position of the cardiac chambers and of their relationship to the great vessels. An evaluation of the vascularity of the lungs may be helpful in deciding whether or not there is a reduction or an increase in pulmonary blood flow or pulmonary arterial pressure.

The greatest advances in the field of radiology have been derived from the roentgenoscopic visualization of the cardiac chambers and the large vessels (angiocardiography). Angiocardiography is an extremely valuable adjunct in the diagnosis of congenital heart disease. It is of particular importance in the recognition of transposition of the great vessels and of valvular pulmonic stenosis; these are malformations in which catheterization of the heart, fluoroscopy and clinical examinations all too often fail to arrive at a correct diagnosis.

#### PHYSIOLOGIC TESTS

The purpose of physiologic studies in malformations of the heart is twofold. They should be of aid in the preoperative diagnosis of congenital malformations and they should contribute to the understanding of the disturbances in the internal environment.9 One of the more interesting questions arising in congenital heart disease deals with the adaptation of the organism to anoxemia of long duration. Another problem is concerned with adjustments of the peripheral vascular bed to changes in the systemic flow. In congenital heart disease with cyanosis anoxemia is the result of the intracardiac shunt which increases the gradient between the oxygen tension in alveolar air and that of arterial blood. 16a (Fig. 1.) In contrast, anoxemia encountered in normal individuals exposed to high altitude is the result of a decrease in partial pressure of oxygen of inspired air. (Fig. 1.) In congenital heart disease with cyanosis the bicarbonate content of blood is reduced, together with the carbon dioxide tension, and the blood pH is maintained at normal levels. 16a The gradient in oxygen pressure from arterial to capillary

blood is reduced in patients with congenital heart disease with cyanosis as well as in individuals exposed to high altitude. (Fig. 1.) Polycythemia does not appear to be a necessary requirement for the well-being of anoxemic patients suffering from congenital heart disease.

It was stated before that the anoxemia and consequently the cyanosis are the result of the intracardiac shunt which increases the gradient between the oxygen tension in alveolar air and that of arterial blood. This was expressed by the author in 1948 to make it clear that a decrease in pulmonary blood flow alone does not necessarily lead to arterial oxygen unsaturation. 16a The term "effective pulmonary blood flow" as contrasted to "total pulmonary blood flow" was introduced to indicate that the only "effective" portion of blood coursing to the lung is mixed venous blood which can undergo aeration in the lung.18 It was stated that it is the percentage of total mixed venous blood which is aerated in the lung which determines peripheral arterial oxygen saturation. The means of mathematical expression of this concept appear immaterial 16b as long as one keeps the fundamental fact in mind that a reduction in pulmonary flow alone does not result in anoxemia and cyanosis.

A series of physiologic tests have been adapted to aid in the diagnosis of congenital heart disease. Since they will be discussed in a subsequent review, they will be mentioned only briefly.

Catheterization of the Heart. This is one of the most valuable procedures. The following criteria should be observed: (1) The catheter should be moved under fluoroscopic visualization only. (2) Blood pressures should be recorded from all chambers of the heart and great vessels. (3) The oxygen content of blood in the various chambers of the heart, superior and inferior vena cava and, if possible, the pulmonary artery or the aorta should be determined. Normally, there is very little difference in the oxygen content of caval, right auricular, right ventricular and pulmonary arterial blood. (Table 1.) In intracardiac shunt, however, or patent ductus arteriosus, there will be significant differences in oxygen content between the respective chambers of the heart or between the right ventricle and the pulmonary artery. (4) The volume of blood flow through the various portions of the circulatory tree should be calculated by means of the Fick principle. Various formulae describing the measurements of volume flows have been described. Although these calculations should be considered only approximations, a knowledge of the various intra- and extracardiac shunts is of great aid in the understanding of the individual malformation. For example, calculations have shown that in most congenital malformations of the heart in which

Table 1
NORMAL PRESSURES AND OXYGEN CONTENTS

	Pressures (mm. Hg)	Oxygen Contents (vol. %)
Right auricle	5/0	Not well mixed
Right ventricle	25/0	16
Pulmonary artery	25/10	16
Left ventricle	120/0	20

a septal defect is present the volume flow through the shunt is predominately unidirectional. However, in complete or partial transposition of the great vessels a unilateral shunt is incompatible with life since it would lead either to depletion or hypervolemia of either the pulmonary or the systemic circulation.<sup>9</sup>

Exercise Test. The test consists of stepping up and down one step 30 cm. high thirty times in one minute. Normally the pulmonary circulation increases sufficiently to meet the respiratory demands of exercise. 17,18 Therefore the oxygen uptake per liter of ventilation increases during the test. In patients with pulmonic stenosis, however, a sufficient increase in the effective pulmonary blood flow cannot take place, and the ratio oxygen consumed/liter of ventilation (the oxygen equivalent) decreases.9 The test is of value in differentiating congenital malformations of the heart in which the effective pulmonary blood flow is fixed from those malformations in which the pulmonary flow can increase. It should be kept in mind, however, that a fall in the oxygen equivalent may also result from an abnormally large rise in the respiratory minute volume. Nevertheless, in 80 per cent of all patients with pulmonic stenosis in whom the diagnosis was confirmed at operation a fall in the oxygen consumed per liter of ventilation occurred.9

Measurement of Changes in Arterial Oxygen Saturation by Photoelectric Means (Oximetry). This method is particularly useful in conjunction with the exercise test. A fall in the oxygen saturation during exercise is usually indicative of the presence of a right to left shunt. The measurement of arterial oxygen saturation while the patient is breathing pure oxygen is a rough method for differentiation between cyanosis due to anatomic shunts and cyanosis resulting from intrinsic lung disease. In lung disease the shunts are generally not very large and are due to distribution or diffusion difficulties. On breathing pure oxygen the effects of poor distribution of oxygen through the lung and the effect of poor diffusion of oxygen are eliminated and the arterial oxygen saturation reaches normal limits. In the presence of a large anatomic shunt, however, full saturation of arterial blood does not occur. 19a,b

Measurement of Pulmonary Capillary Flow. This represents a rough estimation of the total amount of blood flowing through the lungs. By comparing pulmonary capillary flow as determined by a CO<sub>2</sub> equilibration method and pulmonary artery flow, the volume flow through a patent ductus or through collateral vessels may be estimated.<sup>20</sup>

#### CLASSIFICATION OF CONGENITAL HEART DISEASE

Three different classifications of congenital heart disease have been proposed. Maude Abbott's classification is based on the presence or absence of cyanosis, and congenital heart disease is accordingly divided into three groups: i, an acyanotic group with no abnormal communications; II, a group with arteriovenous shunts who show terminal reversal of flow; III, a group composed of individuals with cyanosis.5 The main disadvantage of this classification lies in the fact that there is considerable overlapping between these groups. For instance, although septal defects are classified as belonging to Group II, cyanosis may never appear. Patent ductus, also included in this group, usually does not lead to cyanosis. Furthermore, cyanosis does not represent the primary physiologic disturbance but is only the result of such disturbances.

Taussig has introduced another classification. <sup>15</sup> Group I, malformations which deprive the body of an adequate amount of oxygenated blood; Group II, malformations which permit the body to receive an oxygen supply sufficient for the growth of the individual. Here, too, the groups overlap. Using this classification, Eisenmenger's complex is brought into Group II despite the fact that in this malformation the arterial oxygen unsaturation may be severe. Furthermore, it has been shown that the organism can get along with an extremely low oxygen tension

in arterial blood. Therefore, an estimation of what constitutes an "adequate" amount of oxygen in arterial blood is difficult if not impossible.

A physiologic classification suffers from the disadvantage that malformations with similar anatomic findings are brought into different physiologic groups. However, it should be kept in mind that surgical intervention depends on physiologic as well as on anatomic findings. Accordingly, in this review cardiac malformations will be classified as follows according to the disturbances in the dynamics which result from these malformations:<sup>9</sup>

- 1. Pulmonary flow less than systemic flow. Pulmonary artery pressure usually decreased.
  - A. Tetralogy of Fallot
  - B. Pseudotruncus arteriosus
  - C. Tricuspid atresia
  - D. Single ventricle
    - 1. With pulmonary artery arising from a rudimentary outlet chamber
    - 2. With pulmonic stenosis
  - E. Transposition of the great vessels with pulmonic stenosis
  - F. Patent foramen ovale with pulmonic stenosis
  - G. Ebstein's disease with patent foramen ovale
  - H. Anomalous venous return
    - 1. Pulmonary arteriovenous fistula
    - 2. Superior vena cava emptying into the left auricle
- II. Pulmonary flow greater than systemic flow and/or pulmonary artery pressure normal or increased.
  - A. Eisenmenger's complex
  - B. Transposition of the great vessels
    - 1. Complete
    - 2. Partial
  - C. Isolated septal defect
    - 1. Auricular septal defect
      - a. Uncomplicated
      - b. Lutembacher's disease
    - 2. Ventricular septal defect
  - D. Aortic atresia with patent ductus arteriosus
  - E. Single ventricle
    - 1. With both great vessels arising from the rudimentary outlet chamber
    - 2. With the aorta arising from the rudimentary outlet chamber
  - F. Truncus arteriosus
  - G. Patent ductus arteriosus

- H. Anomalous venous return with pulmonary veins emptying into the vena cava or the right auricle.
- III. Pulmonary flow equals the systemic flow at rest and after exercise.
  - A. Isolated pulmonic stenosis
  - B. Patent foramen ovale as an isolated anomaly
  - C. Coarctation of the aorta
    - 1. Adult type
    - 2. Infantile type without patent ductus arteriosus
  - D. Double aortic arch

Systemic flow may be defined as the volume of venous blood which returns to the right auricle. It does not, however, represent the aortic flow, which may exceed the systemic blood flow, i.e., in the presence of a large extracardiac left to right shunt. Pulmonary artery blood flow is the volume of blood coursing through the lung through the pulmonary artery alone. The effective pulmonary blood flow is the amount of mixed venous blood which eventually is aerated in the lung.

For the remainder of this review the classification outlined before will be followed, except for the discussion of the anomalies of the venous return. For clarity's sake these malformations will be described together as an anatomic entity.

## Group I. Pulmonary Artery Flow Less Than Systemic Flow—Pulmonary Artery Flow Usually Decreased

Tetralogy of Fallot. This is the most frequent congenital cardiac malformation with cyanosis and includes about 75 per cent of all cyanotic patients with congenital heart disease. It consists of pulmonic stenosis combined with dextroposition of the aorta, a high interventricular septal defect and right ventricular hypertrophy. Usually the pulmonic stenosis is infundibular, involving the musculature of the right ventricle below the pulmonic valve.

The heart is usually of normal size. The contour of the heart is characteristic. In the anteroposterior position there is concavity in the region of the pulmonary conus. In the left anterior oblique position the heart is slightly enlarged anteriorly. The pulmonary window is clear. Examination of the lung field shows reduced hilar vascular shadows.

Figure 2 illustrates the circulatory findings in the malformation. The pulmonary flow is below

normal, the systemic flow may show marked variations, the over-all shunt is from right to left; there may also be some left to right admixture. Postoperatively the total pulmonary blood flow increases and the gradient between right auricular and right ventricular oxygen content may rise. The collateral circulation to the lung, which includes the artificial ductus, increases. In tetralogy of Fallot there is an elevation in the right ventricular systolic pressure but the systolic pressure in the pulmonary artery is below that in the right ventricle. There may be a pressure gradient from the pulmonary artery to the infundibular chamber and from there to the right ventricle. (Fig. 3.) Calculations of volume flows are of particular importance in this malformation. For instance, if the systemic flow preoperatively is very low, the construction of a large shunt through the artificial ductus is not advisable because of the danger of peripheral circulatory failure.

Pseudotruncus is a condition characterized by a high ventricular septal defect with overriding aorta and right ventricular hypertrophy. (Fig. 4.) In contrast to the tetralogy of Fallot the pulmonary artery is atretic and the circulation to the lung is via the bronchial arteries or through a patent ductus arteriosus. The recognition of pulmonary atresia by physiologic tests is not possible. Angiocardiography is of greater diagnostic value than catheterization of the heart.

There is frequently enlargement of the heart. Murmurs are usually systolic but not infrequently there may be a continuous murmur. Such a continuous murmur is usually caused by a patent ductus or by large, tortuous, bronchial arteries. Roentgenography and fluoroscopy reveal findings similar to those recorded in the tetralogy of Fallot except that the typical bootshape of the heart is exaggerated.

In tricuspid atresia with defective development of the right ventricle the primary lesion is atresia of the tricuspid value. (Fig. 5.) The blood is unable to pass through the stenosed or atretic valve and enters the left ventricle either through a patent foramen ovale or an auricular septal defect. To reach the lungs, blood may pass through a ventricular septal defect to the diminutive right ventricle or it may course into the aorta and thence to the lungs through a patent ductus arteriosus or bronchial arteries.

The clinical picture is quite similar to that of the tetralogy of Fallot. Commonly this mal-

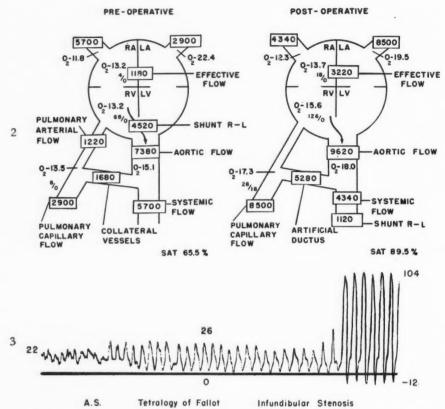


Fig. 2. The preoperative and postoperative circulatory findings in a patient with tetralogy of Fallot.

Fig. 3. Represents a pressure tracing obtained on withdrawal of the catheter from the pulmonary artery through the pulmonic stenosis and through the infundibular chamber into the right ventricle. It may be seen that a pressure gradient exists between the pulmonary artery, the infundibular chamber and the right ventricle.

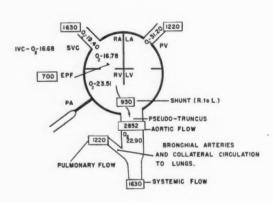
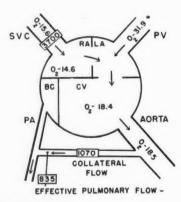


Fig. 4. The circulatory findings in a case of pseudotruncus arteriosus.



\*- CALCULATED BC- BLIND CHAMBER CV- COMMON VENTRICLE

Fig. 5. The circulatory findings in a case of tricuspid atresia.

formation produces even greater incapacity. Cyanosis is often more intense and earlier in onset.

X-ray and fluoroscopy reveal a relatively large left ventricle and a small or absent right ventricle. In the anteroposterior view there is,

an operable malformation in which construction of an artificial ductus increases the effective pulmonary blood flow.

Single Ventricle with the Pulmonary Artery Arising from a Rudimentary Outlet Chamber. In this malformation the rudimentary outlet chamber is

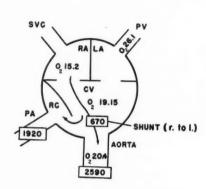


Fig. 6. The circulatory findings in a case of single ventricle with a pulmonary artery arising from a rudimentary outlet chamber.

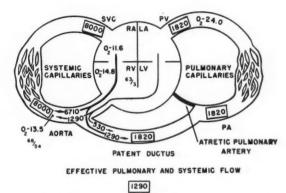


Fig. 7. The circulatory findings in a case of transposition of the great vessels with atresia of the pulmonary artery.

as in the tetralogy of Fallot, a concavity in the region of the pulmonary conus. Beneath this concavity, however, there is a gentle rounding of the cardiac silhouette and the apex frequently extends slightly below the diaphragm. <sup>15</sup> In the left anterior oblique position the heart fails to project anteriorly toward the retrosternal space but projects posteriorly toward the spine. The pulmonary window is clear and the lung fields appear avascular. There is usually left axis deviation and left ventricular preponderance.

Catheterization in this malformation may offer valuable information and greatly aid in the diagnosis. 21 However, if catheterization is to be of value the possibility of the diagnosis must be entertained and the procedure performed with this possibility in mind. The diagnosis of this malformation should be suspected if the catheter enters a high pressure chamber from which blood of relatively high oxygen content is obtained. On withdrawing to the right atrium the catheter tip should pass to a lower pressure area containing blood of a corresponding high oxygen content. Figure 5 shows that the pulmonary blood flow, calculated on the assumption that the pulmonary arterial oxygen content is the same as that of the right ventricle, is decreased. The effective pulmonary artery flow is also reduced. The pressure in the common ventricle is elevated. Tricuspid stenosis or atresia is

separated from the main ventricle by a muscular ridge. The rudimentary chamber lies in the region normally occupied by the pulmonary conus. Pulmonary stenosis may be present. (Fig. 6.)

Because of the presence of a large right to left shunt, anoxemia and cyanosis are usually severe. On fluoroscopy the lungs appear to be avascular. This is an important differential diagnostic criterion because it indicates that it is the pulmonary artery which originates from the rudimentary outlet chamber. In infants the pulmonary conus is usually prominent. As the child grows the conus becomes less prominent in the anteroposterior view.

Usually the catheter does not enter the rudimentary chamber; there is a difference in oxygen content between right auricular blood and blood in the high pressure chamber of more than 3.5 volumes per cent. The over-all shunt is from right to left. (Fig. 6.) Differentiation between tricuspid atresia and this malformation is often difficult. However, differentiation is of importance only for theoretical reasons since both tricuspid atresia and single ventricle with the pulmonary artery arising from a rudimentary outlet chamber are amenable to surgery.

Transposition of the Great Vessels with Pulmonic Stenosis. Accurate diagnosis of this condition is extremely difficult. Fluoroscopy and angio-

cardiography are of greater diagnostic help than catheterization. The lung fields are clear due to the presence of pulmonic stenosis but the heart is usually enlarged—a finding that is uncommon in the tetralogy of Fallot. Despite this, the malformation is frequently diagnosed as tetralogy

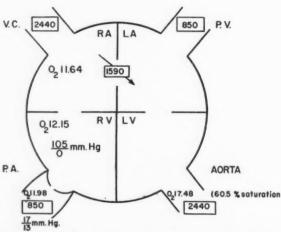


Fig. 8. The circulatory findings in a case of pulmonic stenosis with patent foramen ovale.

of Fallot. The electrocardiogram may show both right and left ventricular hypertrophy.

It has already been stated that in transposition of the great vessels the pulmonary and the systemic circulation exist as separate units; therefore, in order to balance the two circulations, any unilateral shunt has to be compensated by another shunt in the opposite direction. The physiologic findings in one case in which the diagnosis was confirmed by postmortem examination are shown in Figure 7. It may be seen that the volume flows through the systemic and pulmonic circulation, are different. In the case illustrated in Figure 7 the only blood supply to the lung is through a patent ductus arteriosus. The systemic circulation contained 6,710 cc. of unoxygenated blood and only 1,290 cc. of oxygenated blood. It is therefore not surprising that patients with this malformation are severely handicapped.

Pulmonic stenosis with patent foramen ovale has been described by Maraist, <sup>22</sup> Selzer<sup>23</sup> and Mannheimer. <sup>14</sup> Roentgenologic examination seems to be by far the most important clinical diagnostic tool in the differentiation of pulmonic stenosis, with or without patent foramen ovale, on the one hand, and the tetralogy of Fallot on the other. The characteristic features are dilation of the pulmonary conus and marked en-

largement of the right ventricle and auricle, combined with very clear lung fields. The main pulmonary artery and its two main branches may be large but pulsations are absent or minimal. The contrast between the size of the pulmonary artery and the lack of vigorous pulsations is striking.

The circulatory findings are described in Figure 8. It may be seen that there is no significant difference in the oxygen content of blood samples obtained from the right auricle and ventricle. This indicates that the shunt through the patent foramen ovale is entirely from right to left. Peripheral arterial oxygen saturation is reduced as a result of this right to left shunt. The systemic flow is usually normal and the effective and pulmonary artery flows are reduced. The right auricular pressure is increased in patients with this malformation. Pulmonary valvulotomy rather than construction of an artificial ductus is the operation of choice.24 After construction of an artificial ductus the volume of blood returning to the left auricle increases. Due to the limited capacity of this chamber the left auricular pressure rises and prevents the operation of the interauricular vent mechanism, which is responsible for the right to left shunt. This results in a further rise in right auricular pressure which eventually leads to right-sided failure. Such physiologic considerations have been borne out by clinical experience which has shown that creation of an artificial ductus leads to congestive heart failure.<sup>22</sup>

Ebstein's Disease with Patent Foramen Ovale. This malformation, first described by Ebstein in 1866, has as its essential feature a downward displacement of the tricuspid valve in the right ventricle. <sup>25</sup> (Fig. 9.) The tricuspid valve arises partially from the annulus fibrosus and partially from the wall of the right ventricle. Anatomically, therefore, the right ventricle is bisected by the abnormal valve into two chambers, one of which is in direct contact with the right auricle. Usually, the foramen ovale is patent; as a result the arterial oxygen saturation is decreased.

The heart may be enlarged. Cardiac arrhythmias are frequent in this malformation. The electrocardiogram may show changes in the shape of the ventricular complex occurring at regular intervals. <sup>15</sup>

Figure 9 shows that there is also a reduction in pulmonary arterial flow. Usually the pressure in the right ventricle is decreased, probably as a result of hypoplasia of right ventricular muscle.

Group II. Pulmonary Artery Flow Greater Than Systemic Flow and/or Pulmonary Artery Pressure Normal or Increased

Eisenmenger's Disease. This malformation is anatomically identical with the tetralogy of Fallot except that pulmonic stenosis is absent.

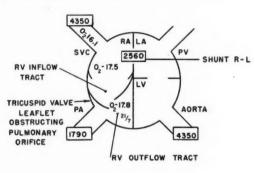


Fig. 9. The circulatory findings in a case of Ebstein's disease.

On fluoroscopy the right ventricle and right auricle are found to be enlarged. The pulmonary conus is convex rather than concave. There may be some enlargement of the left ventricle as well. The lung fields appear abnormally vascular. The pulmonary artery, as a rule, may be seen to pulsate. In some instances the pulmonary artery and its branches may be so large that the diagnosis of Lutembacher's syndrome must be entertained.

Physiologically, it is one of the group of congenital malformations of the heart in which pulmonary hypertension is present. The malformation is extremely rare. The dynamics of this malformation are illustrated in Figure 10. There is pulmonary hypertension as a result of increased resistance in the pulmonary vascular bed.<sup>26</sup> In some patients with this malformation the pulmonary artery flow exceeds the systemic flow; in others the intracardiac shunt is predominately from right to left. Usually the difference between the two volume flows is slight. As a result of the increase in pulmonary resistance the systolic and diastolic pressures in the pulmonary artery are elevated. Lequime,7 Cosby<sup>27</sup> and Soulie<sup>28</sup> reported studies in patients suffering from this malformation. The relationship of this malformation to uncomplicated ventricular septal defect has been discussed by Selzer.29

Complete Transposition of the Great Vessels. Abbott, quoting Vierordt, differentiates four types of transposition:<sup>5</sup> (1) complete transposi-

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tion in which the aorta and pulmonary artery arise from reversed ventricles; (2) partial transposition in which both large vessels arise from the same or from a common ventricle but in a reversed relation; (3) corrected transposition in which each vessel emerges from its own ventricle

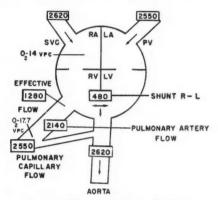


Fig. 10. The circulatory findings in a case of Eisenmenger's disease.

with the ventricles being reversed. Most workers, however, define corrected transposition as complete transposition of the great vessels in which a portion of the pulmonary veins returns to the right auricle or one of its tributaries. The anomalous origin of the aorta to the right of its normal position, commonly known as dextroposition, may be regarded as the first or minor degree of transposition, and is so classified in Maude Abbott's chart.<sup>5</sup>

Complete Uncorrected Transposition. In this condition the aorta arises from the right ventricle, receiving systemic venous blood, and the pulmonary artery arises from the left ventricle, receiving oxygenated blood. Blood pumped out by the left ventricle through the pulmonary artery to the lungs returns via the pulmonary veins to the left auricle. The aorta receives blood from the right ventricle and the blood from the systemic circulation returns to the right auricle. (Fig. 11.) In complete transposition the aorta arises anteriorly and the pulmonary artery posteriorly. The position of the ventricles, however, is not reversed.

If complete transposition is to be compatible with life, other malformations have to exist in order to make possible an exchange between the greater and the lesser circulation. These additional defects may be in the form of an auricular or ventricular septal defect or in the form of a patent ductus arteriosus, which would have to conduct blood from the pulmonary artery into the systemic circulation, and vice versa. The

relative survival time of patients with complete transposition depends on these associated abnormalities.<sup>30</sup> The longest life expectancy is associated with an interventricular septal defect. A patent auricular septum is the next most favorable isolated defect and a combination of

be amenable to surgical treatment. The cyanosis is usually intense and there may be a systolic murmur. The heart is usually enlarged, the pulmonary conus is full and the hilar markings are increased. There are expansile pulsations in the lung fields.

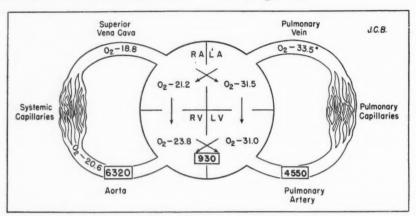


Fig. 11. The circulatory findings in a case of transposition of the great vessels with auricular and ventricular septal defects.

these two gives the best prognosis. The findings in a patient with auricular and ventricular septal defect and transposition of the great vessels are illustrated in Figure 11. Right ventricular pressures are elevated. The oxygen saturation of peripheral arterial blood is markedly decreased. Diagnosis of transposition of the great vessels by catheterization is extremely difficult without advanced knowledge of the nature of the malformation. However, if the aorta is intubated, it is helpful to turn the patient into the right oblique or right lateral position. If the catheter lies anteriorly and in close proximity to the right ventricular outflow tract, the aorta is probably transposed. The main value of catheterization in transposition lies in the recognition of the location of the shunt.31 However, diagnosis is usually possible by means of clinical findings. The heart is usually enlarged, there is severe cyanosis; and since the pulmonary artery is transposed, the pulmonary conus is absent in the anteroposterior position. In younger individuals the change in the relative position of the great vessels causes a characteristic abnormality in their fluoroscopic shadows.16 Usually the lung fields appear abnormally vascular. This is the result of pulmonary hypertension.

Complete Transposition of the Aorta with Overriding of the Pulmonary Artery. Recognition of this malformation is important since clinically it resembles Eisenmenger's complex but may

One case of this malformation has been reported by the author in a joint paper with Helen B. Taussig.<sup>32</sup> Figure 12 describes the dynamics in this malformation. The oxygen content of pulmonary arterial blood significantly exceeds that of right ventricular blood. Since clinical findings render the diagnosis of a patent ductus arteriosus unlikely, the diagnosis of an overriding pulmonary artery can usually be made without difficulty. The resistance in the pulmonary arteriolar bed is increased. Without this increased resistance hypovolemia of the systemic circulation and hypervolemia of the pulmonary circulation would ensue. Similar to complete transposition, a unidirectional shunt cannot exist continuously, as it would lead to progressive depletion of the circulating blood volume in either the pulmonary or the systemic circulation. In the case illustrated in Figure 12 the relatively small volume of the left to right shunt furnishes the only means by which oxygenated blood enters the systemic circulation. Bayer has recently published detailed clinical and physiologic findings in a patient suffering from this malformation. 65

Defects of the Auricular and Ventricular Septum. Defects of the auricular and ventricular septum are frequently associated with pulmonary hypertension and increased pulmonary blood flow. 10,33,34

Most fluoroscopic and clinical findings are the result of either pulmonary hypertension or of

increased pulmonary blood flow. The pulmonic second sound is usually loud and snapping. Frequently the right auricle and the right ventricle are enlarged. The pulmonary conus may be prominent and the hilar shadows marked. In patients with small ventricular septal defects these signs may be absent.

Calazel and his co-workers<sup>36</sup> as well as Cournand et al.,<sup>37</sup> Brannon<sup>38</sup> and Sicot<sup>39</sup> have analyzed the pressure relationship in a series of patients with auricular septal defects.

Lutembacher's Disease. Martineau reported the first case of an auricular septal defect with mitral stenosis.<sup>40</sup> The malformation was first

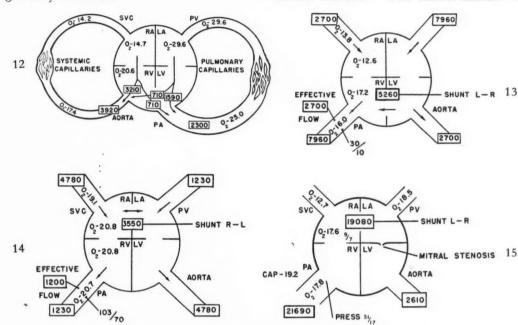


Fig. 12. The circulatory findings in a case of complete transposition of the aorta with overriding of the pulmonary artery.

Fig. 13. The circulatory findings in a case of ventricular septal defect.

Fig. 14. The circulatory findings in a case of auricular septal defect.

Fig. 15. The circulatory findings in a case of Lutembacher's disease.

Figure 13 illustrates the point that ventricular septal defects are usually characterized by a gradient in oxygen content from right auricular to right ventricular blood; in auricular septal defects the gradient in the oxygen content is between caval and right auricular blood. (Fig. 14.) In auricular as well as ventricular defects the over-all shunt is usually from left to right, but in some instances, depending upon the relative resistances of the pulmonary and systemic vascular beds, the shunt may be from right to left. Differential diagnosis between a patent ductus and high ventricular septal defect by catheterization is sometimes difficult. This is because some of the oxygenated blood of the pulmonary artery may regurgitate into the right ventricle, increasing the gradient between the oxygen contents of right auricular and right ventricular blood. Opdyke and his group have performed extensive studies of the dynamics of artificially produced septal defects in dogs.35

described in detail by Lutembacher in 1916.41 He expressed the opinion that the defect of the interauricular septum relieves the strain of mitral stenosis and thereby increases life expectancy. He was, therefore, the first to direct attention to the difference in dynamics between mitral stenosis alone and mitral stenosis with auricular septal defect. The circulatory findings in patients with Lutembacher's syndrome are illustrated in Figure 15. There is usually a very large shunt from left to right through the auricular septal defect; as a result, the pulmonary blood flow is greatly increased. This increase in pulmonary blood flow is responsible for the prominence of the pulmonary conus and of the marked pulsations in the lung fields. It has been shown by Calazel that in patients with Lutembacher's disease the left auricular pressure exceeds that in the right auricle. 36 However, the pulmonary artery pressure is usually only slightly elevated. In only one of five cases of

Lutembacher's disease seen by the author was pulmonary hypertension present.

As a result of the tremendous increase in pulmonary flow there is usually enlargement of the right auricle and ventricle and of the pulmonary arteries. The latter may show aneurysmic

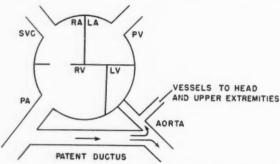


Fig. 16. The circulatory findings in a case of aortic atresia with patent ductus arteriosus.

dilatation. The size of the left auricle is also increased.

Aortic Atresia with Patent Ductus Arteriosus. This is an extremely rare malformation. The primary malformation consists of defective development of the aortic orifice. The left ventricle may be absent or there may be a thinwalled poorly developed chamber. Figure 16 illustrates the circulation in this malformation. If the left ventricle is absent, the mitral valve is atretic and there is a defect in the auricular septum. The direction of the shunt through the auricular defect is entirely from left to right, and the blood reaches the aorta via the pulmonary artery and a patent ductus arteriosus. The malformation is the direct mirror image of tricuspid atresia. The blood supply to the myocardium, to the head and to the upper extremities is derived from the blood which has coursed through a patent ductus arteriosus. This blood, of course, has a low oxygen saturation and consequently cyanosis will be present. Dyspnea is usually severe. Cardiac failure usually ensues early in life. There is usually enlargement of the right auricle and ventricle and the pulmonary arteries. There is right axis deviation. 15 It should be kept in mind that these changes are the result of the presence of a patent ductus which shunts blood from the pulmonary artery to the aorta. Therefore, the work of the right ventricle is greater than that of the left, leading to right ventricular hypertrophy.

Single Ventricle. This malformation is always associated with a rudimentary outlet chamber which represents the bulbus cordis. The follow-

ing malformations are included in this category: (1) single ventricle with both vessels originating from a rudimentary outlet chamber; (2) single ventricle with the aorta arising from the rudimentary outlet chamber; (3) single ventricle with pulmonic stenosis and (4) single ventricle

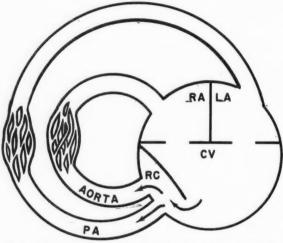


Fig. 17. The circulatory findings in single ventricle with both vessels originating from a rudimentary outlet chamber.

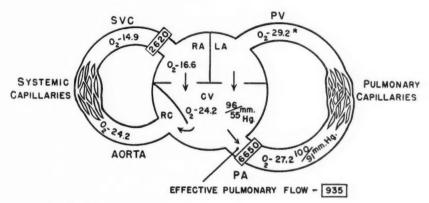
in which the pulmonary artery arises from a rudimentary outlet chamber. The last two malformations have already been discussed.

1. Single ventricle with both vessels originating from a rudimentary outlet chamber: The clinical diagnosis of this malformation is based on fluoroscopy or x-ray findings. 15 Figure 17 illustrates the point that because of the narrow passage between the main and rudimentary chambers the volume flow in both great vessels must be reduced. Furthermore, if the resistance in the pulmonary vascular bed is less than that in the systemic circulation, the pulmonary artery flow must exceed the systemic flow. The aorta is transposed to the right and blood from the systemic circulation is returned to the right auricle via the systemic veins. (Fig. 17.) Physiologically, therefore, this malformation represents a partial transposition. There is marked prominence of the pulmonary conus in infancy, and cyanosis and anoxemia are severe. The condition is rarely compatible with a life expectancy of more than a few months. 15

2. Single ventricle with a rudimentary outlet chamber from which the aorta arises: Since the rudimentary outlet chamber is always the bulbus cordis, the aorta and pulmonary artery are both transposed. Therefore the malformation might be called single ventricle with transposition of

the great vessels. The pulmonary artery originates posteriorly from the main chamber, the aorta originates anteriorly from the rudimentary outlet chamber. The path of the circulation in this malformation is illustrated in Figure 18. The oxygen content of ventricular blood

the left anterior oblique position is of diagnostic significance. <sup>15</sup> Furthermore, there is enlargement of the aorta which produces an indentation of the esophagus along its left margin, displacing it toward the spinal column. In older individuals the cardiac contour may resemble



\* - CALCULATED

RC - RUDIMENTARY CHAMBER

CV- COMMON VENTRICLE

Fig. 18. The circulatory findings in a case of single ventricle with the aorta arising from a rudimentary outlet chamber.

markedly exceeds that of right auricular blood. Furthermore, the oxygen content of the pulmonary arterial blood is even higher than the oxygen content of blood in the high pressure chamber. Pressures in the ventricle and in the pulmonary artery are elevated. It is significant that as a result of the origin of the aorta from the rudimentary outlet chamber the systemic flow is considerably less than the pulmonary artery flow.

As a result of the right to left shunt, the oxygen saturation in peripheral arterial blood is reduced. Due to the large pulmonary blood flow, the lung fields are vascular on fluoroscopy. Sometimes the aorta may be seen to arise anteriorly. In infants the rudimentary outlet chamber causes a prominence of the pulmonary conus; in older individuals this chamber is no longer visible. 15

Truncus Arteriosus. True truncus arteriosus is a rare malformation. The pulmonary artery rises from a single vessel which overrides both ventricles. Physiologically this malformation resembles pseudotruncus arteriosus except that in true truncus 1 or 2 pulmonary arteries arise from the common trunk. Diagnosis by fluoroscopy is usually not too difficult. The heart is enlarged and there are marked pulsations in the lung field. In infants the shape of the heart in

that found in the tetralogy of Fallot with extreme pulmonic stenosis. 15 The findings in a case of physiologic truncus arteriosus are illustrated in Figure 19. In this patient the circulation to the right lung was through a large bronchial artery, that to the left through a patent ductus arteriosus. There was a large gradient between the oxygen content of right auricular and right ventricular blood and a smaller gradient between the oxygen content of right ventricular blood and the blood of the vessel emanating from the ventricle. Apparently, in this patient the pulmonary blood flow exceeded the systemic flow. As a result of the large effective pulmonary blood flow, the arterial oxygen saturation was not very low. Soulie and co-workers described studies in a number of patients with various types of truncus arteriosus. 42

Patent Ductus Arteriosus. This malformation is included in this group since the pulmonary capillary flow exceeds the systemic flow. The malformation consists in a communication between the pulmonary artery and the aorta with a shunt coursing usually from the aorta to the pulmonary artery. Due to the absence of a right to left shunt, cyanosis and arterial unsaturation are absent.

The principal finding in this malformation is a loud, roaring continuous murmur over the

base of the heart. Due to the presence of the large left to right shunt, the pulse pressure is usually increased. There is sometimes a femoral and brachial thud and a demonstrable capillary pulse. The electrocardiogram is usually normal and abnormalities in the electrocardiogram

malformation. The oxygen content of pulmonary artery blood is greater than that of right ventricular blood. Due to the presence of pulmonic insufficiency some of the oxygenated blood may regurgitate into the right ventricle, simulating the presence of a ventricular septal

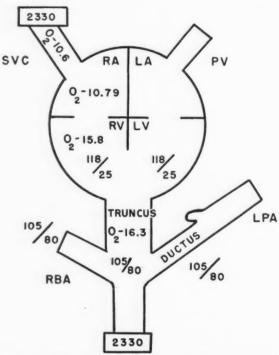


Fig. 19. Illustrates the circulatory findings in a case of physiologic truncus arteriosus, confirmed by autopsy; the circulation to the left lung is through a patent ductus arteriosus, that to the right lung through a large bronchial artery. The pressures in the common ventricle and those in the aorta are approximately equal.

suggest other cardiac malformation. Fluoroscopic and x-ray findings usually show great variations in the contour of the heart and it is believed by Lynxweiler and Wells that the diagnosis of patent ductus arteriosus is not justified on the basis of fluoroscopy and roentgenologic findings alone. 43 Subacute bacterial endarteritis may be associated with patent ductus arteriosus. Although the statistical incidence of subacute bacterial endarteritis is not certain, it can be said that until the age of thirty or thirty-five years probably from 20 to 25 per cent of patients with patent ductus arteriosus will succumb to this complication. 44 Patent ductus arteriosus may be also associated with other congenital malformations, such as auricular or ventricular septal defect. Figure 20 describes the course of the circulation in this

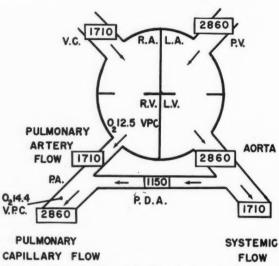


Fig. 20. The circulatory findings in a case of patent ductus arteriosus.

defect. The aortic flow is considerably greater than the systemic flow and the pulmonary capillary flow exceeds the right ventricular outflow. Usually the flow through the ductus comprises about 40 per cent of the left ventricular output.

Findings have been published on patients in whom the pulmonary arterial pressure exceeded that in the systemic circulation and the blood flow through the ductus coursed through the pulmonary artery into the aorta.8,9,45-47 In Johnson's patient there was an intermittent reversal of flow through the ductus. DuShane and Montgomery described a case of a ten year old child in whom cardiac catheterization indicated the presence of a patent ductus arteriosus and pulmonary hypertension. 48 Dammann, Berthrong and Bing reported on four patients in whom the pressure in the pulmonary artery was at least equal to that encountered in a systemic artery. 49 Diagnosis of this interesting malformation may be obtained by intubation of the ductus or by comparison of the oxygen saturation of blood in the right brachial artery and in one of the femoral arteries. Due to the reversed flow through the ductus, the oxygen saturation of femoral arterial blood is below that of right brachial arterial blood.

Group III. Pulmonary Flow Equals the Systemic Flow at Rest and during Exercise

Isolated congenital pulmonary stenosis may be defined as a stenosis of that vessel unassociated with any abnormal communications between the greater and lesser circulation. The

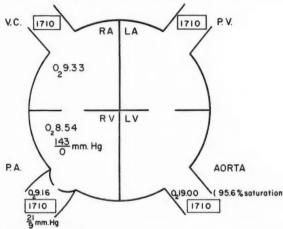


Fig. 21. The circulatory findings in isolated congenital valvular pulmonary stenosis.

stenosis may be located at the infundibular area of the right ventricle but usually affects the valve itself (valvular stenosis as compared to infundibular stenosis). There is hypertrophy of the right ventricle. The pulmonary artery beyond the stenotic valve may be greatly dilated, sometimes to twice the normal diameter or more. Cyanosis may or may not be present in this malformation. Among the cases collected by Greene, cyanosis was present in only twenty-eight of sixty-four patients. Papers dealing with this malformation have been published by Larson, 50 Maraist,<sup>22</sup> Greene,<sup>51</sup> Silber,<sup>52</sup> Dow<sup>53</sup> and Pollack.<sup>54</sup> In most of these studies except in those of Maraist, the diagnosis was not confirmed by autepsy. The circulation in this malformation is illustrated in Figure 21. There is no significant change in the oxygen content of blood samples obtained from any chamber of the heart or the pulmonary artery, indicating the absence of a left to right shunt. Since the peripheral arterial blood is fully saturated, a right to left shunt is not present. The systemic, effective and pulmonary artery flows are equal. There is a marked elevation of the right ventricular pressure. The right auricular pressure is also increased. Differentiation of this malformation from the tetralogy of Fallot is of importance because construction of an artificial ductus arteriosus is not indicated in valvular pulmonic stenosis with closed foramen ovale because the ratio of effective pulmonary over systemic blood flow is unity. Pulmonary valvulotomy introduced by Brock appears to be the operation of choice.<sup>24</sup>

In a series of ten patients with this malformation studied postoperatively, the right ventricular pressure decreased, although not to normal

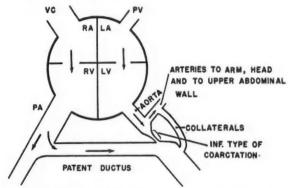


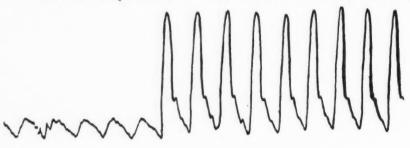
Fig. 22. The circulatory findings in a case of infantile type of coarctation of the aorta.

values. The pulmonary blood flow showed no constant changes. However, as a result of the fall in right ventricular pressure, the work of the right ventricle decreased postoperatively.

Coarctation of the Aorta. An infantile and an adult type of coarctation must be distinguished. In the infantile type there is a diffuse narrowing of the aorta between the origin of the left subclavian artery and the point of entrance of the ductus arteriosus. (Fig. 22.) In the adult type there is a localized constriction of the aorta which usually occurs above the point of entrance of the ductus arteriosus. In the infantile type of coarctation the constriction usually causes complete interruption of the aorta; prior to the development of collateral vessels, the circulation to the lower extremities is through a patent ductus arteriosus. The signs and symptoms of the two types of coarctation of the aorta are identical if, in the infantile type, the ductus undergoes obliteration. On the other hand, if the ductus remains patent, cyanosis will be present below the iliac crests due to shunting of unsaturated blood into the aorta through the ductus. 15 Two patients with the infantile type of coarctation and ductus arteriosus have been described by Taylor and his associates. 45 Soulie described findings in two patients with this malformation.55 The clinical findings in the adult form of coarctation are well known. The arterial oxygen saturation is normal since there is no intracardiac shunt. There is hypertension in the upper extremity and either normal or reduced blood pressure in the lower extremities.

The pulse pressure in the legs is decreased. Not infrequently the pulses in the right and left arm are unequal. The size of the heart may be within normal limits or show hypertrophy of the left ventricle. There is usually a systolic murmur. Extensive collateral circulation produces a

isolated patent ductus arteriosus. In the latter condition the output of the left ventricle exceeds that of the right since blood courses from the systemic to the lesser circulation. In contrast, the blood flow through the ductus is reversed in the malformation under discussion. Therefore



S. H. PRESSURE DISTAL: 93/72 PRESSURE PROXIMAL: 220/78 mm. Hg. Fig. 23. Pressure tracing obtained from a catheter in the aorta. The sudden changes in systolic pressure occur as the catheter tip passes through the area of coarctation (explanation in text).

series of signs which are characteristic of this malformation. Intra-arterial aortography or intra-arterial catheterization are sometimes of value in the localization of the coarctation. It is sometimes possible to pass the catheter tip from the thoracic aorta through the coarctation into the aorta distal to the stenosis. (Fig. 23.) The tracing from the proximal portion of the aorta shows widening of the pulse pressure, systolic hypertension and a peculiar double dicrotic notch which has been observed repeatedly by the author on several similar occasions. The tracing from the distal aorta shows the typical damped tracing previously reported. <sup>56</sup>

The etiology of hypertension in coarctation of the aorta was investigated by the author and his co-workers by means of catheterization and other physiologic methods. <sup>56</sup> The conclusion was reached that the hypertension existing in coarctation of the aorta is not necessarily the result of renal factors. However, the question of etiology of hypertension in this malformation is by no means solved. <sup>57</sup>

In coarctation of the infantile type the fundamental feature is a diffuse narrowing of the isthmus of the aorta between the entrance of the left subclavian artery and the point of entrance of the ductus arteriosus. (Fig. 22.) In principle, the malformation results in hemodynamic changes which are the reverse of those seen in

the amount of blood returning to the right auricle is considerably increased and the output of the right ventricle is large.

Abnormalities of the Venous Return. Anomalies of the venous return may result in a right to left or a left to right shunt. Patients in whom the superior vena cava drains into the left auricle and patients with pulmonary arteriovenous fistula belong into the former category. In patients with a systemic arteriovenous fistula and in those in whom all or several veins drain into the right auricle or a tributary thereof, the shunt is from left to right. Anomalous drainage without shunt is present when there is a persistent left superior vena cava.

1. Anomalies of the venous return resulting in a right to left shunt; anomalous drainage of the superior vena cava into the left auricle: Friedlich, Bing and Blount<sup>58</sup> studied three patients with this malformation. Figure 24 illustrates the findings in one of these patients in whom the diagnosis was confirmed at operation. It may be seen that the patient also had pulmonic stenosis. Due to the right to left shunt, there is peripheral arterial unsaturation, which allowed the patient to benefit from the construction of an artificial ductus arteriosus.

Pulmonary Arteriovenous Fistula. The development of large vascular channels between the pulmonary artery and vein results in a charac-

teristic clinical syndrome. Due to the presence of the right to left shunt, there is polycythemia and cyanosis. Dyspnea on exertion may be a prominent symptom. Associated hemangiomas in other parts of the body are frequent. Figure 25 outlines the path of the circulation. The cardiac

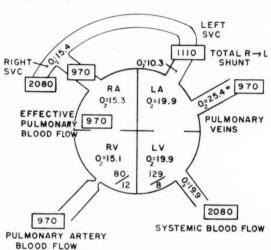


Fig. 24. Circulatory findings in a patient in whom the left superior vena cava entered the left auricle. Pulmonic stenosis is also present.

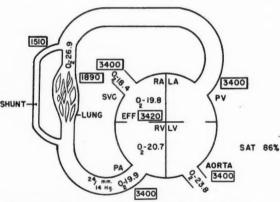


Fig. 25. The circulatory findings in a patient with pulmonary arteriovenous fistula. The cardiac output in this patient is normal; the arterial oxygen saturation is decreased. Approximately 40 per cent of the pulmonary artery flow is shunted through the fistula.

output in this patient is normal despite the fact that 42 per cent of the pulmonary artery flow is shunted through the fistula. Denolin and his coworkers, as well as Baker, described findings in patients with a pulmonary arteriovenous fistula in whom the cardiac output was increased. <sup>59,60</sup> The difference between the pulmonary artery flow and the effective pulmonary blood flow represents the volume of blood shunted through the pulmonary arteriovenous fistula. Calculations of the vascular resistance through the

fistula and through the remainder of the pulmonary vascular bed show that, as in the case illustrated in Figure 26, the total pulmonary resistance is normal, while the resistance of the lung exclusive of the fistula is slightly elevated; the resistance of the pulmonary arteriovenous

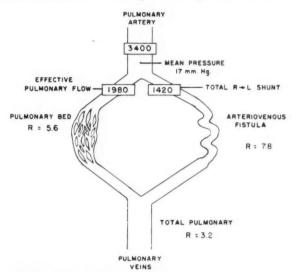


Fig. 26. The relationship of pressure, corrected vascular resistance and flows in a patient with pulmonary arteriovenous fistula.

fistula is almost twice the normal pulmonary resistance. (Fig. 2.) Similar findings were described in the other patients with this malformation. The increase in the vascular resistance of the lung exclusive of the fistula leads to an increase in the amount of the right to left shunt, a decrease in the effective pulmonary blood flow and hence to greater arterial oxygen unsaturation. The reason for the increase in the vascular resistance of the lung exclusive of the fistula is not known. There may be an anatomic increase in the pulmonary resistance due to multiple small thrombi. On the other hand, the increase in pulmonary arteriolar resistance may be caused by hypoxemia. Such a mechanism has been described by Motley et al.61 and by Liljestrand.62 If this is the case, a vicious circle may be established. Peripheral arterial oxygen unsaturation augments pulmonary arteriolar resistance, increases the blood flow through the fistula, thus further increasing peripheral arterial unsaturation.

2. Anomalies of the venous return constituting a left to right shunt; systemic arteriovenous fistula: The findings in a patient with this malformation are described in Figure 27. This condition produces a left to right shunt allowing oxygenated blood

to return to the right auricle. The hemodynamic changes produced have been described in detail by Cohen<sup>63</sup> and by Warren and their associates.<sup>64</sup> In contrast to pulmonary arteriovenous fistula, peripheral arteriovenous fistula is almost always accompanied with an increase in the

the pulmonary vein is catheterized directly, a diagnosis of interauricular septal defect may be falsely made. The over-all dynamic effect is similar to an auricular septal defect; there is a left to right shunt with increased pulmonary blood flow. Pulsations in the lung fields may be

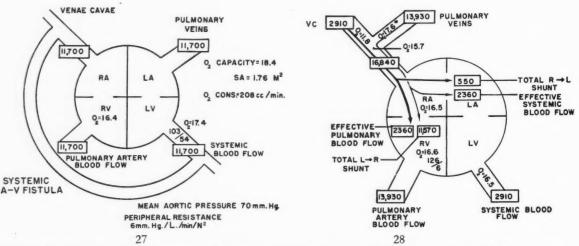


Fig. 27. The findings obtained in a patient with peripheral arteriovenous fistula. The cardiac output is increased in this malformation and the oxygen saturation in peripheral arterial blood is normal. Right auricular pressure is usually normal.

Fig. 28. Circulatory findings in a patient in whom all pulmonary veins drained into the superior vena cava. A patent foramen ovale is also present. The oxygen contents of blood in all cardiac chambers are identical, and the pulmonary flow is markedly increased. (Courtesy of the *Bull. Johns Hopkins Hosp.*, vol. 86, no. 1, 1950, Johns Hopkins Press, Baltimore, Md.)

cardiac output of major proportions which may lead to cardiac hypertrophy and congestive failure.

Pulmonary Vein Draining into the Right Auricle or Its Tributaries. Figure 28 illustrates the finding in a patient in whom all the pulmonary veins drain into the superior vena cava. A patent foramen ovale is also present. From the diagnostic standpoint the important features are the evidence of oxygenated blood entering the superior vena cava and the finding of comparable blood oxygen contents in all chambers of the heart, the pulmonary artery and the systemic arteries.

On fluoroscopy patients with this malformation usually show definite right ventricular and right auricular enlargement. The pulmonary conus and the pulmonary arteries are prominent. The most significant fluoroscopic finding is an enlargement of the superior vena cava, with pulsations of this vessel.

If only a portion of the pulmonary veins drain into the right auricle or one of its tributaries, the oxygen content of right auricular blood exceeds that of blood from the vena cava. Unless marked and the pulmonary conus may be prominent. The heart is usually enlarged to the right.

#### CONCLUDING REMARKS

The advances made in the field of congenital heart disease during the last ten years have been rapid and benefits derived for those afflicted with these conditions have been dramatic. It has become apparent that catheterization of the heart and angiocardiography are important supplements to the clinical and radiologic diagnoses of these malformations. However, different and newer tools for further advancement of physiologic and diagnostic evaluation of congenital malformations of the heart are being developed. It is becoming apparent that electrokymography and ballistocardiography may be utilized to great advantage in these studies. The physiopathology of congenital cardiac malformation is still a rapidly expanding field, the progress depending on the ability of those engaged in this work to utilize new and different technics and procedures.

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# Clinico-pathologic Conference

# Coronary Artery Disease with Intra-abdominal Complications

S TENOGRAPHIC reports, edited by Robert J. Glaser, M.D., and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, M. G. (138371), a white married laborer fifty years of age, entered the Barnes Hospital for the first time on August 10, 1946, complaining of pain in the chest. The family history was of interest in that both the patient's mother and father had died of cerebral hemorrhage, and one sister died of tuberculosis. Significant in the past history was the fact that the patient had acquired a penile sore at the age of twenty for which he was given several intravenous injections. Prior to therapy a serologic test was said to have been positive and following therapy it was reported as negative. During the ensuing years on three or four separate occasions he received courses of intravenous injections, but at no time was he ever told that his serologic test was positive. His wife also had had syphilis but she, too, had been treated. The systemic history was not remarkable. The patient had worked as a laborer, had drunk excessively for some time and was a moderate smoker.

Six months prior to entry he suddenly developed pain in the anterior chest which radiated down both arms. The pain increased in intensity and he was seen by a physician who told him that his blood pressure was above 200 mm. of Hg. A diagnosis of coronary artery disease was made, and the patient was kept in bed for an unknown period of time. He recovered and then was apparently well until six days prior to admission when he had a similar attack. His pain was continuous until entry into Barnes Hospital.

Physical examination revealed the temperature to be 36.8°c., pulse 72, respirations 18 and blood pressure 135/85. The patient complained of pain in the chest but he did not appear ill. Examination was entirely negative except that

the liver edge was felt 6 cm. below the right costal margin.

The laboratory data were as follows: Blood count: red cells, 4,150,000; hemoglobin, 13.9 gm.; white cells, 10,400; differential count: within normal limits. Urinalysis: negative. Blood Kahn test: positive. Wassermann reaction: negative. Stool examination: guaiac negative. Electrocardiogram: changes compatible with an acute anterior myocardial infarction.

After entry the patient was placed at bed rest and given medication for his pain. During the remainder of his hospital stay he had no further chest discomfort. Subsequently a lumbar puncture was done with entirely negative findings. The sedimentation rate was mildly elevated. Serial electrocardiograms showed changes characteristic of the evolution of an acute anterior myocardial infarct. The patient was discharged on August 24, 1946, much improved.

Following discharge he had at least ten attacks of severe substernal pain, each of which lasted from one-half to two days. The pain usually radiated down both arms, and on four separate occasions was severe enough to cause the patient to be hospitalized in outside hospitals. Aside from occasional shortness of breath he had had no symptoms of heart failure and he had never been digitalized. His last episode of pain occurred six weeks prior to admission.

One month before entry he developed generalized cramping abdominal pain which localized in the right lower quadrant. Soon after onset of the pain the patient developed diarrhea which persisted. Occasionally the diarrheal stools contained blood, the presence of which was attributed by the patient to hemorrhoids which he had had for many years. On two occasions he was nauseated and vomited

material which contained a considerable amount of fresh blood.

He was seen in an outside hospital where a diagnosis of appendicitis was made and a laparotomy was performed. At operation the appendix was found to be normal, but the terminal ileum was described as "blue in color"; it was not resected. Following the operation the patient continued to have daily attacks of pain in the right lower quadrant for which he was given demerol. At times the pain radiated to the back and to the right testicle. It was not related to meals and was unassociated with urinary symptoms. Some of the attacks of pain lasted as long as eight to twelve hours and were accompanied with chills, sweating and temperature elevations from 100° to 104°c. At no time was he jaundiced.

One week before his second admission to the Barnes Hospital the patient left his home to go to another large medical center. While enroute he developed another attack of chest pain for which he was hospitalized in a nearby hospital, and on August 13, 1941, he was transferred to the Barnes Hospital for further study.

At the time of entry the patient's temperature was 37.4°c., pulse 90, respirations 24 and blood pressure 130/64. He appeared well developed and well nourished and was in no apparent distress, but he was somewhat confused about the sequence of events which had transpired immediately before entry. Examination of the pupils showed them to be round, regular and equal. They reacted sluggishly to light. Aside from moderate arteriolar narrowing and A-V nicking the fundi were negative. Examination of the upper respiratory tract was negative. The neck veins were not distended. Examination of the chest revealed increased breath and voice sounds over the right apex posteriorly where ronchi were also heard. Otherwise the lungs were clear. The heart was not enlarged and the sounds were of good quality. The rhythm was regular and there was a grade I apical systolic murmur which was not transmitted. The abdomen was slightly distended. Localized tenderness and rebound tenderness were noted in the right lower quadrant, but there was no resistance to palpation at that site. The liver edge was again felt 6 cm. below the costal margin. It was smooth and slightly tender. The remainder of the abdominal examination was negative. Rectal examination revealed external hemorrhoids and moderate prostatic enlargement.

The deep tendon reflexes were hyperactive but neurologic examination was otherwise negative.

The laboratory data were as follows: Blood count: red cells, 4,130,000; hemoglobin, 12.9 gm.; white cells, 12,300; differential count: stab forms 2 per cent, segmented forms 62 per cent, lymphocytes 32 per cent; monocytes 4 per cent. Urinalysis: negative. Stool examination: negative for occult blood and for parasites. Blood cardiolipin tests: all negative. Blood chemistry: total proteins, 6.3 gm. per cent; albumin, 4.0 gm. per cent; globulin, 2.3 gm. per cent; cephalin-cholesterol flocculation test, negative; thymol turbidity, 4.3 units. Corrected sedimentation rate: 40 mm. per hour. Sputum examination: no acid-fast bacilli. Roentgenogram of the chest: there was a calcified primary complex in the right middle lobe, but otherwise the lung fields were clear. Flat films of the abdomen were negative. Electrocardiogram: changes consistent with an anterior myocardial infarction of uncertain duration were noted. In addition there were ventricular premature contractions.

On the second day after entry the patient suddenly had a shaking chill and his temperature rose to 40°c. He complained of pain in the chest with radiation down both arms, but the pain was not relieved by either demerol or nitroglycerin. Concomitantly he had generalized pain throughout the abdomen with which were associated nausea and vomiting. Physical examination revealed no new findings. The blood pressure was 122/64. The heart sounds were of good quality with an occasional ventricular premature contraction, and there was slight tachycardia. A repeat white blood cell count at this time was 34,250, the differential showing 92 per cent polymorphonuclear cells. The patient's fever persisted for several hours and then his temperature fell precipitously to normal. Blood smears during the episode were negative for malarial parasites.

The following day physical examination revealed that the tip of the spleen had become palpable. The patient was improved in that his chest pain had subsided. The white blood cell count was now 22,600, and urinalysis was negative. Repeated examination of the abdomen revealed generalized tenderness but no point of localization. When the patient had improved further, intravenous pyelography was done. It indicated excellent function and normal configuration of the kidneys, and it was not believed

that the genitourinary tract could be implicated in the patient's symptoms. Further urine examinations were negative for bile pigments and for porphyrins. A number of blood cultures was negative. Agglutination tests against typhoid and paratyphoid antigens were negative, and a tuberculin skin test was negative.

On the eighth hospital day a gastrointestinal x-ray series was performed. The upper gastrointestinal tract was normal, and motility in the small intestine was normal. The distal 10 to 12 inches of the terminal ileum appeared distinctly abnormal on both the three- and fivehour films. There was an absence of normal mucosal pattern, and it was suggested that the findings were consistent with hyperplastic lymphoid tissue; a diagnosis of regional ileitis was made. A twenty-four-hour film showed complete absence of barium in the small bowel, and a barium enema revealed an entirely normal colon. Oral cholecystograms were negative. Additional electrocardiograms revealed little change from the one obtained on entry.

Because of the findings noted on the gastrointestinal x-ray examination and the fact that the patient's pain had become constant and increasingly severe, it was decided to submit him to abdominal exploration. It was realized that he was an extremely poor surgical risk. Fifteen minutes after induction of anesthesia, achieved with a combination of sodium pentothal,® nitrous oxide, ethylene and ether, the patient developed acute pulmonary edema. Anesthesia was discontinued, measures to combat pulmonary edema were instituted and the patient was returned to his room. The abdominal pain continued unabated and tenderness was noted over the entire left upper quadrant, but there was no distention. The liver edge could be felt 12 cm. below the costal margin. Removal of 600 cc. of urine by catheterization gave no relief. The usual therapy for cardiac failure resulted in marked improvement in this aspect of the patient's condition.

Late in the evening of the day on which exploration had been attempted, the patient's temperature was 36.5°c., the pulse 100 and the blood pressure 96/80. On the following day he was more comfortable although marked tenderness in the upper quadrant persisted. The splenic edge could not be felt. The red blood cell count was 4,000,000 with 11.8 gm. of hemoglobin, and the white blood cell count was

15,000, the differential showing 5 stab and 55 segmented forms. A few rales were heard at both lung bases.

One week later the patient again developed severe pain in the chest. Rales became numerous throughout both lungs and positive pressure oxygen, morphine and aminophyllin were administered without effect. The patient became extremely apprehensive, refused to tolerate an oxygen mask and his respirations rose to 40 per minute. He developed carpopedal spasm and had a generalized convulsion. His color became ashen gray, his lips cyanotic, and despite all attempts at resuscitation, he expired on September 4, 1951.

#### CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: It is quite clear that this patient had severe coronary artery disease, but the nature of his intra-abdominal disease is not nearly so obvious. Both the internist whose patient he was, and the surgeon who saw him in consultation, believed that exploratory laparotomy was indicated. Operation was attempted but the patient developed acute pulmonary edema during the induction of anesthesia, and the contemplated surgery could not be performed. I believe we should consider the nature of the patient's abdominal pain in order to see if it helps us in reaching a diagnosis. First, however, I would like to have Dr. Elliott comment on the findings of the gastrointestinal x-ray examination.

DR. GLADDEN V. ELLIOTT: The stomach, duodenum and jejunum appeared normal. However, on the films made three and five hours after ingestion of the barium meal, there was a definite abnormality of the distal ileum. (Fig. 1.) This segment, measuring 10 to 12 inches in length, was narrowed, retained barium poorly, and had an abnormal mucosal pattern. The changes ended abruptly at the ileocecal junction. There was no alteration of motilitybarium reached the ascending colon at three hours—and all the barium was within the colon at twenty-four hours. A barium enema done subsequently revealed no abnormalities of the colon although barium could not be freely refluxed into the ileum.

Roentgenologically, therefore, we demonstrated a cicatrizing, non-obstructive lesion involving the distal 10 to 12 inches of the terminal ileum, a finding characteristic of regional or terminal ileitis. However, the history



Fig. 1. X-ray film of the terminal ileum taken five hours after ingestion of barium. Note the narrowing of the lumen.

in this particular case does not seem to fit that diagnosis too well, and clinically the diagnosis of mesenteric vascular occlusion was considered. From the roentgenologic point of view, mesenteric occlusion is usually associated with ileus of varying degree, resulting in gaseous distention and definite delay in intestinal motility. This case presents the converse of those findings, and it is difficult to reconcile them with that diagnosis. It should be pointed out, however, that roentgenologic experience, especially with barium meal examinations, is practically nonexistent in mesenteric vascular occlusion. Patients with acute occlusion are seldom examined and few of them live beyond the acute episode. If this lesion was produced by a mesenteric vascular occlusion, it represents, in our experience, a new roentgenologic entity.

DR. ALEXANDER: At the time the patient was operated upon at an outside hospital because of presumptive appendicitis, the appendix was found to be normal, but the terminal ileum was described as being blue in color. Dr. Scheff, do you agree that this patient had terminal ileitis?

DR. HAROLD SCHEFF: No, I do not. In my opinion the history is not consistent with that diagnosis. I believe this patient had several vascular lesions, either thrombotic or embolic, to different segments of the small intestine.

DR. ALEXANDER: What specifically makes you think the patient did not have terminal ileitis; his diarrhea, fever and x-ray findings were all compatible with it.

DR. Scheff: The fact that he vomited blood is against the diagnosis. Further, the terminal ileum was described as being involved for about 12 inches. With that much involvement, I would have expected to be able to palpate a mass in the right lower quadrant since the process is usually hyperplastic. Finally, it is very unusual for patients over fifty to have terminal ileitis.

DR. SAMUEL C. BUKANTZ: Was there any further information about the gross appearance of the terminal ileum other than that it was blue in color?

DR. ALEXANDER: That was the only statement in the report we received from the outside hospital where the operation was performed.

DR. Scheff: The blue color described is not consistent with terminal ileitis.

DR. ALEXANDER: What color would you expect?

DR. Scheff: Red rather than blue.

DR. ALEXANDER: What type of pathologic process could give rise to a blue color?

DR. Scheff: I would think in terms of alteration in the circulation to the involved segment.

DR. ALEXANDER: Dr. Hagemann, when you first saw this patient, what was your impression?

DR. PAUL O. HAGEMANN: As you mentioned at the outset, it was apparent that this patient had severe coronary artery disease with several old infarctions and probably a recent one. On the basis of the infarctions, we postulated that he had mural thrombi and embolization of the intestinal tract.

Dr. Alexander: Do you agree with this concept, Dr. Kenamore?

DR. BRUCE D. KENAMORE: I certainly believe the patient had vascular disease. I would agree with Dr. Scheff that regional ileitis is unlikely.

DR. ALEXANDER: Dr. Mendeloff, do you have anything to add?

DR. ALFRED I. MENDELOFF: There is one disease which could explain all the findings in the terminal ileum, namely, lymphosarcoma. I would like to ask Dr. Elliott whether he thinks the films are compatible with that diagnosis.

DR. ELLIOTT: It could not be ruled out on the basis of the x-ray findings.

DR. ALEXANDER: In terminal ileitis, it is my impression that the lesion is primarily one of lymphocytic infiltration.

DR. MENDELOFF: The site of the lesion is in the submucosa, and hyperplasia of lymphatic tissue leads to encroachment on the lumen. Certainly the involved area in terminal ileitis is not blue.

DR. ALEXANDER: Dr. Kenamore, considering further the diagnosis of terminal ileitis, which I believe is important because of the signs of definite inflammatory disease, I would like to ask you whether you think that there was an associated complication such as abscess or perforation. You will recall that the patient had a leukocytosis of 35,000, that he probably had had fever for a month and that he had constant pain. Are all of these findings compatible with terminal ileitis?

DR. KENAMORE: A very common complication in terminal ileitis is development of fistulas, usually to adjacent viscera. When present, fistulas may lead to peritoneal irritation, and even peritonitis by perforation is not uncommon. The clinical picture described would have been compatible with the presence of such a fistula.

DR. Scheff: In my experience perforation with formation of a large abscess is uncommon in terminal ileitis. Also, extreme leukocytosis would be an unusual finding under those circumstances.

DR. ALEXANDER: Are there any further comments?

DR. MENDELOFF: In regard to the question of vascular occlusion which was brought up, I believe it should be pointed out that there may be a difference between the clinical picture in mesenteric venous occlusion and mesenteric arterial occlusion. Frequently venous thrombi recanalize and there may be no infarction of the bowel. On the contrary, with arterial occlusion, which is much more apt to give rise to the type of picture seen here, there is usually infarction of the intestine.

DR. EDWARD MASSIE: Is the vomiting of blood in keeping with arterial occlusion?

DR. MENDELOFF: Yes.

DR. Kenamore: Another evidence of embolization was the fact that the spleen suddenly became enlarged.

DR. ALEXANDER: Is arterial occlusion more common than venous occlusion?

DR. Mendeloff: In this age group, particularly in the absence of previous surgery, arterial mesenteric occlusions are probably more frequent.

DR. ALEXANDER: In the majority of cases is not the superior mesenteric artery involved?

DR. MENDELOFF: Yes, I believe that it is involved in about 90 per cent of the cases.

DR. ALEXANDER: Earlier, Dr. Hagemann, you suggested that the embolus may have come from a mural thrombus in the ventricle. Did you consider the possibility that the lesions may have been due to thrombosis *per se* in view of the fact that the patient had so much arteriosclerosis?

DR. HAGEMANN: We certainly believed that he would have arteriosclerotic changes in the abdominal vessels as well as in the coronary vessels, but nonetheless, we thought that the process was embolic. In this regard, it seems likely to me that there may be gradations of arterial insufficiency. Lesser ones might give rise to clinical signs which are less obvious than those which we usually associate with arterial occlusion.

Dr. Scheff: Such a syndrome has been described recently.

DR. ALEXANDER: It is important in this regard that the patient's symptoms continued for a month, and during this period he apparently had no signs of obstruction. What would you expect to find radiologically in the presence of arterial mesenteric occlusion, Dr. Elliott?

DR. ELLIOTT: One would expect to see marked dilatation and definite delay in motility.

DR. THOMAS H. HUNTER: I know of one instance in which a patient had an arterial vascular occlusion, conclusively evidenced by the passage of tissue per rectum which was demonstrated microscopically to be intestinal mucosa. The patient, who had severe mitral stenosis with multiple emboli, survived the mesenteric occlusion but died later from another cause.

DR. ALEXANDER: I gather then that despite certain features which are rather unusual, the general consensus is that this patient may have had an arterial mesenteric occlusion.

DR. Scheff: In passing one should suggest one other possibility which is much less likely. When multiple thromboses occur, one thinks of carcinoma of the body or tail of the pancreas. The lesions associated with that tumor are venous rather than arterial; but since we are not positive that this man's lesions were arterial, the diagnosis should be mentioned.

DR. CARL G. HARFORD: I think the general consensus is probably correct, but the possibility of amebiasis should come to mind in a patient who has bloody diarrhea, pain in the left lower

quadrant, fever and leukocytosis. Amebiasis is not common in the terminal ileum, however, and it would not explain the hematemesis.

DR. ALEXANDER: How frequently, Dr. Dammin, does amebiasis involve the terminal ileum alone?

DR. GUSTAVE G. DAMMIN: Very rarely, if ever. DR. ALEXANDER: We are faced with the paradox that the x-ray findings are compatible with terminal ileitis but are not particularly in keeping with a vascular lesion; yet, the clinical findings are not considered to be those of

regional ileitis.

DR. MENDELOFF: On that basis I made the suggestion earlier of lymphosarcoma with associated venous mesenteric occlusions. Such a lesion could have explained many of the findings in this case.

Dr. Bukantz: I should like to offer an additional suggestion which comes to mind because this patient had fever, chills, leukocytosis and was seriously ill. I wonder if pyelophlebitis should not be considered. It seems conceivable to me that a granulomatous process involving the terminal ileum may have become complicated by thrombosis of the venous system, ultimately leading to pyelophlebitis.

DR. ALEXANDER: I should like to ask Dr. Bricker, who saw this patient in surgical consultation, to comment on the problem as he

saw it.

DR. EUGENE M. BRICKER: Because the findings at the time of previous exploration at the outside hospital suggested definite disease in the terminal ileum, we thought the possibility that this lesion arose on the basis of something other than a vascular lesion merited serious consideration. I based my opinion partly on the fact that I have never seen a patient with an arterial embolism in the superior mesenteric artery, or anywhere else in the gastrointestinal tract, survive for a month, particularly with the picture which this patient presented. I believed that his entire illness, with the exception of the obvious myocardial infarction, resulted from a lesion in the small intestine, and believed that even though the patient was a poor risk, operation was merited. We had proposed to do the simplest procedure possible, namely, simple diversion of the fecal stream with isolation of the involved segment. If feasible, of course, resection of the involved bowel would have been done, either at the time of the first operation or at a subsequent one.

DR. ALEXANDER: Dr. Massie, the problem of the surgical risk entailed in a patient with coronary artery disease is an important one which we face from time to time. Would you comment on this problem?

DR. MASSIE: Patients with active coronary artery disease in my opinion constitute the most unsatisfactory type of risk. Most other cardiacs do surprisingly well. This patient certainly would have been an extremely poor risk.

DR. ALEXANDER: Is cardiac decompensation, not due to coronary disease, equally serious?

DR. Massie: It is certainly serious, but I do not think to the same degree as is coronary disease. Usually such patients can be compensated, and then subjected to surgery; many do well. Needless to say, surgery in cardiac patients should only be done when it is urgent, but that situation does arise from time to time.

DR. ALEXANDER: Under what other circumstances are patients with cardiac disease particularly poor operative risks, assuming that in each case the operation is essential?

DR. MASSIE: Patients who are cyanotic are, of course, also undesirable risks.

DR. ALEXANDER: What about patients with mitral stenosis?

DR. MASSIE: All other things being equal, there is always a problem of embolization during the procedure, but in general, patients with mitral stenosis do fairly well.

DR ALEXANDER: This patient apparently was in as good condition as possible when he was taken to the operating room and went through the first stage of anesthesia satisfactorily. Subsequently, after anesthesia had been induced, he developed pulmonary edema. Could you give us your opinion as to the mechanism of this occurrence?

DR. Massie: The two complications which are most commonly seen in patients with active coronary disease under anesthesia are pulmonary edema and ventricular arrhythmias. I believe that pulmonary edema probably arises on the basis of decreased cardiac output in a fashion analogous to that which produces paroxysmal nocturnal dyspnea in patients who are asleep and whose heart rate is relatively slow.

DR. ALEXANDER: Dr. Eastwood of the Division of Anesthesiology is here, and I would like him to comment on the general problem presented in this case. Perhaps he would also comment on the choice of anesthetics under such circumstances.

DR. DOUGLAS EASTWOOD: First of all, I would certainly agree with Dr. Massie that patients with coronary disease constitute the worst anesthetic risks we encounter. Their chances for survival, all other things being equal, are much less than any other group of patients. In regard to the choice of anesthetic, I would consider several factors, namely, an anesthetic which would allow as high oxygen tension as possible, one which would avoid a prolonged stage of excitation and one which would not depress the circulation as do large doses of barbiturates. This patient, for example, was given oxygen for ten or fifteen minutes before the anesthetic was started. I believe that that particular measure is worth while since many cardiac patients receive oxygen prior to coming to the operating room and then are without it for a significant period en route. Reinstitution of oxygen therapy may afford some measure of safety. Unfortunately, the patient was placed in a supine position without elevation of the head. Actually, in retrospect, it probably would have been better for him to have been in Fowler's position initially. From the standpoint of the choice of the anesthetic agent, cyclopropane would have offered certain advantages, namely, a high oxygen concentration, rapid induction and prompt recovery. On the other hand, this patient had had an arrhythmia previously and cyclopropane is notable for its tendency to cause arrhythmias. Ethylene permits a rather rapid, simple induction for ether, and it was therefore used initially in combination with ether. At the same time pentothal was available; and when the patient got slightly excited, he was given small amounts of this short-acting barbiturate to get him through the excitement stage. At that point, however, he developed rales in his chest, and it is possible that even the small amount of pentothal which he received depressed the circulation sufficiently to give rise to failure.

DR. ALEXANDER: As I understand it, after the development of signs of pulmonary edema, anesthesia was discontinued. What did you do then?

DR. EASTWOOD: He was given intravenous aminophyllin and oxygen and responded satisfactorily.

DR. HENRY A. SCHROEDER: In regard to the barbiturates I should like to point out that a recent study on the use of sodium amytal was notable in that decreased cardiac output resulted when the drug was used.

DR. ALEXANDER: I believe we all would agree that this patient had severe coronary artery disease which was complicated by arterial mesenteric occlusion. No one seems willing to support the diagnosis of terminal ileitis; and although several other possibilities in regard to the etiology of the intestinal lesion have been mentioned, vascular disease is thought to be the most likely.

Clinical Diagnoses: Myocardial infarctions; multiple mesenteric arterial occlusions.

#### PATHOLOGIC DISCUSSION

DR. MENARD C. IHNEN: The heart was enlarged to a weight of 500 gm. In the posterior interventricular septum there were red-brown and gray-yellow areas which were thought grossly to be recent infarcts. At the apex in the anterior septum and the anterior wall of the left ventricle (Fig. 2) gray scarring with an overlying partially organized and endothelialized thrombus 1 cm. in diameter represented a healed infarct and mural thrombus. The coronary arteries were quite sclerotic with occlusion of the descending branch of the left coronary artery by an old thrombus and of the right artery by a recent thrombus. There were 800 cc. of clear fluid in both pleural spaces, and the congested and edematous lungs weighed 2,000 gm. The liver and spleen were also enlarged and grossly congested. A depigmented infarct involved approximately a third of the spleen, and there was a thrombus in a branch of the splenic artery.

The only significant intestinal lesions were in the distal 40 cm. of the ileum. The wall of the intestine (Fig. 3) was thickened and the outer surface dull and opaque. In the lumen (Fig. 4) the submucosa was 4 mm. thick and the mucosa was red and granular, but there were only a few shallow ulcers. The adjacent mesenteric segment was grey and thickened and the lymph nodes were rather prominent. In a major branch of the superior mesenteric artery to the involved intestine there was a partially organized thrombus. The mesenteric veins were not remarkable, and there was no ascites or acute peritonitis.

Dr. Dammin: The gross appearance of the intestinal lesion was compatible with regional or cicatrizing enteritis; however, a number of clinical and pathologic features of this case were definitely atypical. In large series of cases the average age of the patients with regional enteritis is twenty-seven years with 90 per cent of the

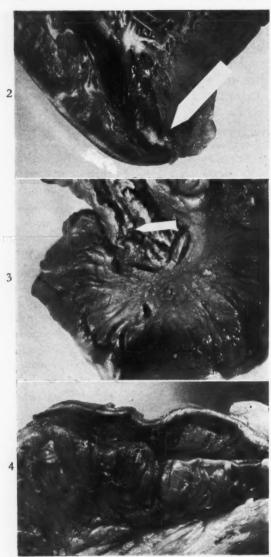


Fig. 2. An old infarct of the anterior septum and wall of the left ventricle with a partially organized mural thrombus in the heart that was possibly the source of emboli to the splenic and mesenteric arteries.

Fig. 3. The thickened and discolored segment of terminal ileum; the pointer indicates the severed branch of the mesenteric artery that was filled by an organized thrombus.

Fig. 4. The irregular fibrous thickening of the serosa, the intact muscularis, the greatly thickened submucosa and the dark granular mucosa of the involved segment; this appearance is compatible with that of lesions from typical cases of regional enteritis.

cases occurring before the age of thirty-five. The ileum is involved in 90 per cent of cases and additional areas of the intestinal wall in 10 to 20 per cent. Peritoneal adhesions and fistulas are commonly prominent features. Arterial occlusions, as far as I have been able to find out,

are not described in regional enteritis although venous thromboses are often recognized. In the present case the patient's age was over fifty years, only one continuous segment of the terminal ileum was involved, there were no adhesions or fistulas, and there was an arterial occlusion but no venous occlusions.

Regional enteritis is a clinical entity with fairly constant features, but faced with a case such as this we have reason to doubt that all similarly appearing lesions of the terminal ileum represent a pathologic entity. There are proponents for each point of view. Ginzburg and Oppenheimer<sup>1</sup> and DeCourcy<sup>2</sup> have described lesions due to vascular insufficiency following strangulated hernias or thrombi in mesenteric vessels which resembled the lesions in regional enteritis. Warren and Sommers<sup>3</sup> on the other hand are of the opinion that the lesions represent a pathologic entity. In this case we examined the thrombosed mesenteric vessel, the infarct and mural thrombus in the heart, and the infarct in the spleen for microscopic evidence of coincidence that might suggest all those lesions were related.

First, from our general knowledge of the progress of events in an infarct we can assume the infarct in the spleen required at least six to eight weeks to attain the state of depigmentation seen at autopsy. Second, by microscopic examination of the superior mesenteric artery at the point of occlusion (Fig. 5) we find preservation of the inner elastic membrane, no intrinsic vascular disease in the form of an arteritis and no appreciable amount of arteriosclerotic alteration; yet the lumen is occluded by an organized and recanalized thrombus. For a thrombus to arrive at this stage of recanalization requires at least six to eight weeks. These two lesions, therefore, could have arisen from emboli released at about the same time. The partially organized mural thrombus in the heart is of similar age, judging by the amount of organization by fibrous tissue and the degree of endothelization of the surface, and represents a possible source of such emboli.

<sup>&</sup>lt;sup>1</sup> GINZBURG, L. and OPPENHEIMER, G. D. Non-specific granulomata of the intestines. *Ann. Surg.*, 98: 1046, 1933.

<sup>&</sup>lt;sup>2</sup> DECOURCY, J. L. J. Med., 15: 216, 1934. Quoted by SHAPIRO, R. Regional ileitis, a summary of the literature. Am. J. M. Sc., 198: 269, 1939.

<sup>&</sup>lt;sup>3</sup> WARREN, S. and SOMMERS, S. C. Cicatrizing enteritis (regional ileitis) as a pathologic entity. *Am. J. Path.*, 24: 475, 1948.

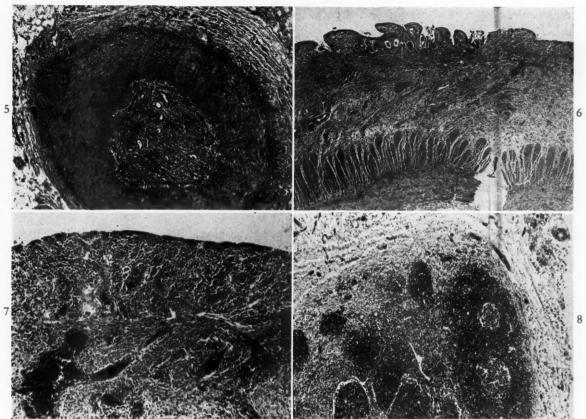


Fig. 5. An organized and recanalized thrombus in the mesenteric artery; the lack of evidence of arteriosclerosis or arteritis suggests this originated as an embolic occlusion.

Fig. 6. The intestinal segment at low magnification. The denuded mucosa, marked cicatricial thickening of the submucosa and lack of focal granulomas are the most significant features apparent.

Fig. 7. Denuded mucosal layer of the involved segment showing its resemblance to granulation tissue.

Fig. 8. A mesenteric lymph node with chronic non-specific inflammation and none of the granulomas sometimes seen in typical cases of regional enteritis.

In Figure 6 the great thickening of the wall of the involved segment of the ileum, particularly the submucosa, is illustrated. The mucosa has only a few thickened villi and is largely denuded of epithelium. These features are compatible with regional enteritis. A more highly magnified illustration (Fig. 7) shows a denuded granulating surface with many small capillaries intensively infiltrated with lymphocytes, plasma cells and eosinophils. A few giant cells are present, but there are no granulomas in the submucosa such as are often prominent in typical regional enteritis. The mesenteric lymph nodes in regional enteritis are often scarred and show the same tubercle-like structures that are seen in the intestinal wall, but Figure 8 shows only a chronic non-specific inflammatory reaction in such a node from this case.

In the heart there are lesions of various ages. Recent thrombi associated with intramural hemorrhage are present in sections from the JANUARY, 1952

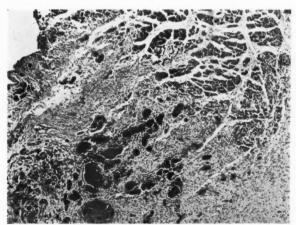


Fig. 9. Junction of old and recent infarcts of the myocardium; the latter had not yet developed an inflammatory infiltration and represented the terminal event.

right coronary artery, and the major trunk of the left anterior descending artery is filled with an organized and recanalized thrombus. The extensive infarcts are of several ages. Figure 9 is

representative of the junction of one area of totally destroyed myocardium representing a process of several weeks' duration, with an area in the upper right corner where there are necrotic myocardial fibers but the necrosis is so recent there is not even an inflammatory response. The latter is probably the lesion responsible for the terminal clinical events. There were obviously numerous bouts of occlusion and myocardial infarction. The old thrombus in the left coronary artery and the lesions of the anterior apex of the heart are of a stage comparable with that due to the occlusion of the superior mesenteric artery, that is, six or eight weeks or older.

Grossly and even microscopically the intestinal lesion in this case might be called regional enteritis. However, the apparent ages of the thrombus in the superior mesenteric artery, the mural thrombus in the heart, and the infarct in the spleen are compatible with the clinical history of the onset of abdominal disease seven weeks before death. It therefore is our interpretation that the pathogenesis of this lesion consists of the sequence of a myocardial infarct, formation of a mural thrombus, emboli to the mesenteric artery and a vascular insufficiency of the wall of the ileum sufficient to cause destruction of the mucosa and subsequent scarring due to both the ischemic necrosis and invasion by enteric bacteria. We have not been able to find morphologic reports of cases that

have survived occlusion of the mesenteric artery and developed lesions in the intestine after an interval of several weeks, but Ross4 described a case in which an exploratory laparotomy exposed a thrombus in the superior mesenteric artery and gross discoloration of the bowel, yet the patient survived without resection of the lesion. Guaiac-positive stools in that case suggested ulceration of the involved mucosa, and the reports of DeCourcy<sup>2</sup> and Ginzburg and Oppenheimer<sup>3</sup> describe destruction of the mucosa by similar means. The later formation of a localized, continuous cicatrix without focal granulomas in such a segment appears logically to be expected. This possibility and the features of this case cited earlier as atypical of regional enteritis suggest the lesion is related directly to the vascular occlusion.

Final Anatomic Diagnoses: Arteriosclerosis of the coronary arteries with occlusions by organized and recent thrombi; old and recent infarcts of the myocardium with a mural thrombus; occlusion of a branch of the superior mesenteric artery by an organized thrombus; cicatrix and stenosis of a segment of the terminal ileum.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

<sup>4</sup> Ross, G. G. Mesenteric thrombosis. *Ann. Surg.*, 72: 121, 1920.

# Research Society Abstracts

## American Federation for Clinical Research

ABSTRACTS OF THE PAPERS PRESENTED AT THE NATIONAL MEETING HELD IN ATLANTIC CITY, MAY 1, 1951

TISSUE SODIUM, POTASSIUM AND MAGNESIUM IN HUMAN HYPERTENSIVE SUBJECTS. Louis Tobian, Jr., M.D. and John Binion, M.D. (introduced by Charles H. Burnett, M.D.), Southwestern Medical School, Dallas, Tex.

In hypertensive human renal arteries obtained at autopsy the sodium content of the medial and intimal layers was 22 per cent higher (p = .001) and the water content 17 per cent higher (p = .001) than in normotensives. These increases could not be correlated with peripheral edema or with the time interval between death and tissue removal. Psoas muscle similarly analyzed showed a 22 per cent higher sodium content (p = .02) in hypertensives than in normotensives. There was no significant difference between normotensives and hypertensives in potassium or magnesium content of arteries or muscle. In brain, right auricle or bladder no significant differences between hypertensives and normotensives were found. The data gave no clue as to how much of the increased sodium and water in hypertensive artery and muscle is intracellular. These human renal arteries contained large amounts of sodium compared to other tissues. Rat aorta is also rich in sodium. The sodium: potassium ratios in normotensive rat tissues obtained immediately postmortem were: aorta, 2.14; quadriceps, 0.14; bladder, 0.78; heart, 0.23; and brain, 0.37. The ratio is unusually high in rat aorta and cannot be explained as a plethora of extracellular fluid. This high sodium content of blood vessels, especially in hypertensives, could conceivably be related to the known influence of dietary sodium on vascular peripheral resistance. If the excess sodium and water in hypertensive renal arteries were also present in the arterioles, the vessel walls might easily swell enough to narrow the lumen and significantly increase peripheral resistance.

FLUID AND ELECTROLYTE BALANCE DURING RECOVERY FROM HIGH OUTPUT HEART FAIL-URE DUE TO BERIBERI. H. M. S. Uhl, M.D., (by invitation) L. C. Alexander, M.D., (by invitation) R. S. McCaughey, M.D., (by invitation) A. J. Boyle, M.D., (by invitation) L. T. Iseri, M.D. and G. B. Myers, M.D., Wayne University College of Medicine, Detroit, Mich.

In a previous study made during recovery from low output failure, cellular uptake of potassium and sodium and loss of water were demonstrated and attributed to inactivation of cellular base. In a case of high output failure due to beriberi studies of Na, K, Cl, N and H2O balance were carried out for a two-day control period and a ten-day therapeutic period in which the only treatment was massive vitamin therapy including 600 mg. of thiamine daily. Daily urinary output and weight loss doubled immediately after institution of thiamine. Intracellular as well as extracellular water balance was negative. Sodium excretion increased immediately to reach a maximum on the fifth day. Cells took up sodium during maximal diuresis but subsequently released most of the uptake. Potassium balance was negative for the first two days of treatment due to the diuresis with high urinary concentrations, but thereafter a markedly positive balance was established by reduction in urinary concentration and resulted in cellular uptake of potassium. Nitrogen balance was consistently negative throughout the study. Hemodynamic studies at the end of the control period confirmed the high output failure and repetition after vitamin therapy showed nearly normal findings. The cellular uptake of potassium and sodium and release of water during recovery from high output failure was comparable to that demonstrated during recovery from low output failure and likewise attributed to inactivation of cellular base. It is postulated that during development of congestive failure osmotic activation of cellular base occurs, followed by uptake of water and expulsion of sodium to balance the rise in osmotic force of the deranged

LIFE SPAN OF THE RED BLOOD CELL IN LEUKE-MIA AND POLYCYTHEMIA. N. I. Berlin, M.D., J. H. Lawrence, M.D. and H. C. Lee, M.D., (introduced by Stewart Wolf, M.D.) University of

California, Berkeley, Calif.

Both N<sup>15</sup>- and C<sup>14</sup>-labeled glycine have been shown to be satisfactory for the measurement of the life span of the red blood cell. London et al., using  $N^{15}$  in one patient with polycythemia vera, reported that the life span of the red blood cell was normal. No studies of this type are available in leukemia. Five patients with polycythemia vera and five patients with chronic leukemia were given C14-labeled glycine. Hemoglobin was isolated from the red blood cells and combusted in CO2. The radioactivity of the CO2 was measured in an ionization chamber. The data indicate that in chronic leukemia the life span of the red blood cell varies from 20 to 120 days. This finding suggests that the anemia of leukemia may often be due to a shortened red cell life span and not to a decrease in the rate of production of red blood cells. In polycythemia vera the radioactivity of the hemoglobin shows an early rise, a fall at eight to ten days, followed by a second rise. This may be interpreted as representing the delivery into the peripheral blood of two classes of red blood cells, one having a very short life span of the order of five to ten days, the second from 80 to 120 days. These data are in accord with findings with radioactive iron that the rate of regeneration of hemoglobin is greater than the anticipated 0.8 per cent per day. However, rather than a uniform population of cells, there are two distinct types. Morphologically, separation of the two classes of red cells would be difficult since the short-lived cells represent only a small fraction of the total number.

Oxygen Content of Sternal Bone Marrow and Its Relation to Polycythemic States, to Anemia and to Heart Failure. Arthur J. Samuels, M.D., Hans H. Hecht, M.D., Merrill C. Daines, M.D., (by invitation) and Ceylon S. Lewis, M.D. (by invitation), University of Utah, College

of Medicine, Salt Lake City, Utah.

The oxygen content of sternal marrow blood was compared with that of arterial and with mixed venous blood obtained simultaneously by cardiac catheterization in normal subjects, in patients with chronic lung disease, with and without polycythemia, in patients with "secondary polycythemia" before and after phlebotomy, in patients with anemia and in subjects with congestive heart failure. The oxygen content was measured at rest, on exercise and after inhalation of 100 per cent oxygen. Total blood volume and plasma volume were estimated by

P<sub>32</sub> and T-1824 dilution. In normal subjects at rest sternal marrow oxygen content lies between that of arterial and mixed venous blood. On exercise normal oxygen content in both arterial and marrow samples is maintained, or tends to rise, mixed venous oxygen content tends to fall. In subjects with chronic lung disease and "secondary polycythemia" the bone marrow oxygen content at rest and after exercise differs little from normal absolute values, despite the lowered per cent saturation. In severe chronic pulmonary disease without polycythemia or in polycythemic patients after phlebotomy, and in anemic subjects, bone marrow oxygen content is severely reduced at rest, and falls further on exercise. Low values are likewise encountered in congestive heart failure not due to lung disease. By this method bone marrow blood is taken to represent "bone marrow exit blood" and is considered comparable to venous blood leaving other organs. Correlation of red cell mass estimations with oxygen content in bone marrow in the various groups suggest that "secondary polycythemia" in chronic lung disease serves to "normalize" the oxygen content of bone marrow. HEMATOLOGIC CHANGES WITH ACTH AND

CORTISONE IN RHEUMATOID ARTHRITIS AND ALLIED DISORDERS. Stuart C. Finch, M.D., (by invitation), Charles L. Crockett, Jr., M.D., Theodore B. Bayles, M.D., (by invitation) and Joseph F. Ross, M.D. Evans Memorial, Peter Bent Brigham, and Robert Breck Brigham Hospitals,

Boston, Mass.

The purpose of this study was to clarify the role of ACTH and cortisone in hematopoiesis, and to correlate changes in the peripheral blood, bone marrow, and blood volume during prolonged administration of these hormones. Careful hematologic observations were made during multiple courses of hormone administration to twenty children and adults with "mesenchymal" disease. At appropriate intervals complete peripheral blood studies, bone marrow aspirations, and blood volume determinations with T-1824 dye were performed. Marked reticulocytosis occurred in all patients while enlargement of the circulating erythrocyte mass and return of normal bone marrow morphology occurred only when there was a good clinical response. Polycythemia was not observed, and posttherapy clinical relapse was invariably associated with hematologic relapse. All patients obtained a transient significant polymorphonuclear leukocytosis while lymphopenia was inconstant and

unsustained. Bone marrow eosinophils remained normal in number when there was profound peripheral eosinopenia. Striking hematocrit changes attributed to hemodilution and hemoconcentration were noted. These observations indicate that ACTH and cortisone are not primary erythropoietic "stimulants" but exert their effect indirectly by suppressing an underlying inflammatory process.

TREATMENT OF PERNICIOUS ANEMIA BY ORAL ADMINISTRATION OF VITAMIN B<sub>12</sub> AND GLANDU-LAR MUCOPROTEIN RECOVERED FROM GASTRIC JUICE OF HUMANS. George B. Jerzy Glass, M.D., Linn J. Boyd, M.D. (by invitation) Michael A. Rubinstein, M.D., (by invitation) and Chester S. Svigals, M.D. (by invitation). New York Medical College, Flower & Fifth Avenue Hospitals, and Metropolitan Hospital Research Unit, New York, N. Y.

The weak oral action of vitamin  $B_{12}$  (extrinsic factor) in pernicious anemia is due to its deficient intestinal absorption in this disease. This is caused by the absence of Castle's intrinsic hematopoietic factor from the gastric juice of these patients, as shown by the effectiveness of small oral doses of vitamin B<sub>12</sub> if administered together with a sufficient amount of normal gastric juice. The substance in the gastric juice responsible for intrinsic factor hematopoietic activity, however, has not been identified. Eight patients with proven pernicious anemia in relapse and observed for three to nine months were given daily oral doses of 7 to 30 micrograms of vitamin B<sub>12</sub> to which, after a control period, a daily dose of 50 to 200 mg. of glandular mucoprotein was added. The latter was recovered from gastric contents rich in this substance. In one case in partial relapse the daily dose of 20 micrograms of vitamin B<sub>12</sub> in association with 50 mg. of mucoprotein was insufficient to promote a hematopoietic response. In two other cases the daily administration of 7 to 10 micrograms of vitamin B<sub>12</sub> with 50 to 100 mg. mucoprotein maintained the blood status but was insufficient for promoting a definite hematopoietic response. In the fourth case the daily administration for several weeks of 10 micrograms of vitamin B<sub>12</sub> with 200 mg. of mucoprotein caused an optimal hematopoietic response. In four other cases in complete relapse a suboptimal or optimal response was obtained after a daily dose of 50 to 150 mg. mucoprotein was added to the daily oral dose of 30 micrograms of vitamin  $B_{12}$ . The response was absent or very

weak during the administration of the same dose of vitamin  $B_{12}$  alone. The data suggest that Castle's intrinsic hematopoietic factor is contained in or is identical with the glandular mucoprotein of the human gastric juice.

EFFECTS OF ACUTE HYPOXIA ON THE CIRCULA-TION OF THE DOG. Benjamin M. Lewis, M.D. (by invitation) and Lewis Dexter, M.D. Peter Bent Brigham Hospital and the Harvard Medical School, Boston, Mass.

Dogs were anesthetized with morphineurethane-chloralose. Catheters were inserted into the pulmonary artery and left atria; cannulas were placed into the femoral artery and vein. Pressures were recorded with electromanometers and cardiac outputs estimated by the Fick method. Breathing mixtures containing 2.5 to 10 per cent oxygen were administered. With 10 per cent oxygen for one to five hours, arterial saturation was 50 to 75 per cent, cardiac output remained normal or increased and left atrial and venous pressures remained unchanged. With 2.5 to 5 per cent oxygen for five to twenty minutes, arterial saturation was 4 to 25 per cent. If arterial saturation was approximately 25 per cent, cardiac output increased without an apparent increase in ventricular filling pressure (Group I). When saturation was below 25 per cent, left atrial and sometimes systemic venous pressure rose (Group II). Cardiac output increased in a third (Group IIa). In the others, flow did not increase despite increased left ventricular diastolic filling pressure (Group IIb). Here, sharp reductions in oxygen supply and cardiac work occurred. When left atrial pressures rose to 20 mm. Hg or more, gross pulmonary edema occurred. Pulmonary vascular resistance showed no significant change with hypoxia from the control values. The primary response to hypoxia is an attempt to maintain normal oxygen supply to the tissues by increasing cardiac output. This may or may not be accomplished by an increased ventricular diastolic filling pressure. The end result of severe anoxia is acute left and then right ventricular failure with death in acute pulmonary edema. Hypoxia apparently does not alter pulmonary vascular resistance.

USE OF PRONESTYL IN THE TREATMENT OF CARDIAC ARRHYTHMIAS: CLINICAL AND EXPERIMENTAL OBSERVATIONS: PRELIMINARY REPORT. E. Lee Garlett, M.D., (by invitation) Keehn Berry, M.D., (by invitation) and Samuel Bellet, M.D., Philadelphia, Pa.

Although pronestyl (procaine-amide hydrochloride) has gained considerable popularity in the treatment of cardiac arrhythmias, there are few data available relative to its action and its therapeutic and toxic effects. The present investigation dealt with the intravenous and oral use of this drug in the treatment of sixty instances of ectopic rhythm in forty-one patients. Pronestyl was found of value in terminating both supraventricular ectopic rhythms as well as ventricular tachycardia. The following ectopic rhythms were treated: auricular tachycardia (twelve cases), auricular flutter (eight cases), auricular fibrillation (seven cases), nodal tachycardia (four cases) and ventricular tachycardia (twelve cases) and, in addition, twenty-five patients with multiple ventricular extrasystoles. Pronestyl was effectual in correcting auricular tachycardia and nodal tachycardia in eighteen of twenty-two trials; and in ten of seventeen instances of ventricular tachycardia (in three subjects partial control of the tachycardia was attained). Ventricular extrasystoles were abolished in most of the patients to whom it was administered. There was a notable lack of success in restoring normal rhythm in patients with auricular flutter and auricular fibrillation. Administration of pronestyl by the oral route was effectual in preventing the return of the ectopic rhythm in most of the patients. In addition, clinical and electrocardiographic changes following the intravenous and oral administration of pronestyl were studied in a group of twenty control patients. The most important toxic effects were marked degrees of hypotension in five patients resulting in syncope, convulsive seizures and attacks of coronary insufficiency. The following electrocardiographic effects of toxicity were noted: widening of the QRS complexes and prolongation of P-R intervals. The occurrence of toxic effects was particularly pronounced in older age groups and in patients with severe degrees of myocardial damage. From these studies it was concluded that this drug is a valuable addition to those available for the treatment of rapid ectopic rhythms; its intravenous administration is apparently safer than that of the corresponding effective dose of quinidine.

EFFECTS OF PROTOVERATRINE ON THE CIRCULA-TION IN HYPERTENSION. S. W. Hoobler, M.D., R. W. Corley, M.D. (by invitation) and T. G. Kabza, M.D., University of Michigan, Ann Arbor, Mich.

Protoveratrine, a purified alkaloid of Veratrum album, was demonstrated by Meilman and Krayer to reduce the blood pressure and pulse when injected into hypertensive patients, without production of nausea or vomiting. These studies have been confirmed and extended to include the oral use of the drug in doses of 750 to 1,500 micrograms. Nausea and vomiting are produced in some susceptible individuals but in others the blood pressure is lowered for four to six hours without unpleasant side effects. Chronic administration over periods up to five weeks and as often as three times daily has been successful in moderating severe hypertension as evidenced by home blood pressure readings. Dramatic relief of hypertensive encephalopathy in two patients has been observed. In hypertensive heart disease reduction in heart size, improvement in dyspnea and occasionally disappearance of gallop rhythm has been noticed. During the period of hypotension, oliguria and moderately decreased glomerular filtration rate occurred, while renal blood flow remained constant or increased with consequent reduction in filtration fraction. Blood flow in the extremities was increased. The drug usually augmented stroke volume but effects on cardiac output were variable, as determined by the direct Fick technic. Atropine abolished the bradycardia and increased the blood pressure in some cases. It is concluded that protoveratrine may be an effective drug in the short term treatment of certain severe cases of hypertension, particularly when certain cerebrovascular or cardiac complications are imminent.

MAJOR SURGERY IN PATIENTS WITH HEALED MYOCARDIAL INFARCTION. Charles A. Hannigan, M.D. (by invitation), Felix Wroblewski, M.D. (by invitation) and John S. LaDue, M.D. Memorial Cancer Center, New York, N. Y.

Sixty-one patients proven to have healed myocardial infarcts were subjected to major surgery for cancer. Their preoperative status, operative course and postoperative morbidity and mortality are contrasted with those in a comparable group of patients without demonstrable heart disease. A 30 per cent increase in postoperative medical complications and a 3 per cent increase in postoperative deaths were observed in the cardiac group as compared with the control group. This large percentile increase in postoperative medical complications (due to a greater number of cardiovascular complications) and small percentile increase in operative

risk are discussed from the point of view of age, sex, history of antecedent cardiac and other disease. Also considered are the influence of hypertension, locus of the myocardial infarct, cardiac classification, preoperative preparation, type of surgery and anesthesia and effects of the administration of parenteral fluids and other medications. It is concluded that life-saving major surgery is not contraindicated in patients with healed myocardial infarcts and may be performed under proper circumstances with but a relatively small increased risk.

HEMODYNAMIC EFFECTS OF ACTH, DCA AND CORTISONE COMPARED WITH CONGESTIVE HEART FAILURE. Roy E. Albert, M.D. and Warren W. Smith, M.D. (introduced by Saul J. Farber, M.D.), New York University College of

Medicine, New York, N. Y.

The relative importance of decreased cardiac output, altered renal hemodynamics and hormonal influences in initiating and sustaining the syndrome of congestive heart failure remains unknown. Since certain features characteristic of congestive heart failure have been seen in some patients treated with ACTH, DCA and cortisone, it seemed desirable to determine, in subjects without heart disease, whether the hemodynamic changes produced by these drugs are similar to those observed in naturally developing congestive heart failure. Hemodynamic determinations have been made on nine noncardiac patients, five treated with ACTH, three with DCA and one with cortisone. Marked peripheral edema developed in five subjects, three of whom also showed minimal respiratory symptoms. These five subjects developed the following hemodynamic changes characteristic of congestive heart failure: increased right atrial pressure, increased right ventricular pressures, increased blood volume and elevation of the arterial pressure. However, no uniform change in cardiac output or A-V O2 difference was observed. The remaining four patients did not develop edema, showed only a small or moderate increase in weight and did not develop the hemodynamic changes present in the edematous subjects. The evidence thus far suggests that when these drugs produce marked edema the accompanying hemodynamic effects simulate the changes usually seen in congestive heart failure, with one striking difference, the cardiac output is not lowered.

CARDIAC ASTHMA: AN EXPERIMENTAL STUDY. John J. Curry, M.D. and Hyman Rubitsky, M.D.

Georgetown University Medical Center, Washington, D. C.

For more than a century it has been assumed that cardiac asthma is a phase of bronchial asthma in which the precipitating factor is congestive failure. However, little investigation of this problem has been made. In the past we have carried out pulmonary function studies including expiratory velocity, vital capacity and maximum breathing capacity in several hundred patients with bronchial asthma or the history of bronchial asthma. In addition we have measured the response to the parenteral administration of histamine and methacholine and the blocking action of sympathomimetic amines and anticholinergic and antihistaminic drugs. A pattern of reaction has been developed by which we were enabled to identify subjects with bronchial asthma. The details of these observations and the methods of study have been published. In the present investigation similar tests were carried out in over forty patients with heart disease, both compensated and decompensated and with and without wheezing. In some instances studies were made before and after recovery from congestive failure and again after "salt loading" of these subjects. While further studies are needed, the results already obtained indicate clearly that wheezing in congestive failure is frequently not related to an underlying asthmatic diathesis. This probably explains why epinephrine g ves little relief from symptoms in the majority of cases.

OXYGEN REMOVAL, OXYGEN CONSUMPTION AND VENTILATION IN NORMAL AND CARDIAC MALE SUBJECTS, DURING THE BASAL STATE AND THE FIRST MINUTE RECOVERY FOLLOWING STANDARD EXERCISE. Edward H. Hale, M.D., (by invitation) John B. Johnson, M.D. and Eugene Clark, Jr., M.D. (by invitation), Howard Uni-

versity, Washington, D. C.

A study of oxygen removal, oxygen consumption and ventilation per minute/BSAM² was made in normal and cardiac subjects in the basal state and during each of the first to four minutes following exercise. The exercise consisted of having the subject stand from the sitting position twenty times in one minute. Expired air was analyzed in duplicate using the Scholander gas analyzer. Normal and cardiac subjects were evaluated clinically by electrocardiogram, cardiac surface area and vital capacity. The basal oxygen consumption in normal subjects was 124 ± 12 cc. and 420 cc.

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during the first minute recovery. In cardiac subjects the mean oxygen consumption in the basal period was 142 cc. but was the same as the normals in the first minute recovery period (415 cc.). Hyperventilation was present in cardiac subjects during both the basal and recovery periods. The basal ventilation in normal subjects was 2.84 ± 0.5 L., first minute recovery 7.25 ± 1.29 L. The mean ventilation for cardiacs in corresponding periods was 5.64 L. and 10.9 L., respectively. The basal oxygen removal in normal subjects expressed cc. per L. ventilation was 44.3 ± 4 and 58.6 ± 6 during the first minute recovery. The corresponding mean values in cardiacs was 26.0 cc. or 59 per cent of normal and 38.9 or 68 per cent normal; 10 (oxygen consumption L./min./M²) (oxygen removal cc./100 cc. ventilation)2 was evaluated as a means of assessing cardiac insufficiency. This study appears to provide an accurate technic in assessing cardiac insufficiency.

AFFERENT LOOP STUDIES AFTER SUB-TOTAL GASTRIC RESECTION. Stanley H. Lorber, M.D. and Harry Shay, M.D. (by invitation), Samuel S. Fels Research Institute, Temple University School

of Medicine, Philadelphia, Pa.

Some complications which follow gastric resection for ulcer present difficult diagnostic problems. Roentgen examination of the stomal area may be unsatisfactory and demonstration of the afferent loop by routine methods is difficult or impossible. To delineate more clearly the stomal area and to obtain complete filling of the afferent loop with barium, a special intubation technic was devised by which a more comprehensive roentgen study was obtained. Two patients recently observed continued to have ulcer symptoms in the right upper quadrant following sub-total gastric resection. In both an exclusion operation had been performed and gastric secretion had been little affected by the procedure. Because some pathologic disturbance was suspected in the "stump" area not demonstrated by routine roentgen methods, an intubation study was performed. In one a "stump ulcer" (duodenal) was revealed and in the other a deformed stump area was delineated which later was proven to be due to invagination of the cuff and associated severe duodenitis. In another patient the clinical diagnosis of perforation of the stump was confirmed by the described technic. One patient with typical symptoms of marginal ulcer was studied after a negative routine roentgen examination. The

excellent mucosal detail obtained by the intubation method clearly revealed marginal ulceration. A larger group of patients subjected to gastric resection and who have remained well have also been studied.

EFFECT OF ACTH UPON THE FECAL LYSOZYME TITER IN ULCERATIVE COLITIS. Robert W. Reifenstein, M.D., John A. Benson, Jr., M.D. (by invitation) and Seymour J. Gray, M.D., Peter Bent Brigham Hospital and Harvard Medical

School, Boston, Mass.

The fecal lysozyme activity was determined by the viscosimetric method of Meyer in fourteen patients with acute ulcerative colitis and in nineteen patients in the chronic phase of the disease. ACTH was administered to five patients in doses of 80 to 160 mg. daily for four to eight weeks and the effect upon the fecal lysozyme titer and the activity of the disease was determined. The fecal lysozyme titer paralleled the clinical course of the ulcerative colitis, decreasing with remissions and increasing with exacerbations. The mean lysozyme titer was 109 units per gm. during the acute phase, decreasing to 12 units during the remission period, compared with the average normal of 4 units per gm. A persistent and often dramatic fall in the fecal lysozyme titer occurred within four to seventeen days of ACTH treatment and coincided with the clinical improvement of the patients. The titers decreased from initial levels of 97 to 291 units per gm. to 7 to 9 units per gm. within four to seventeen days of ACTH administration. The consistent decrease in fecal lysozyme observed in patients responding to ACTH therapy may reflect the inhibitory effect of ACTH upon the inflammatory response of the tissue.

Sustained Contraction of the Colon in Nonspecific Ulcerative Colitis. Fred Kern, Jr., M.D., Thomas P. Almy, M.D., Frank K. Abbot, M.D. and Morton D. Bogdonoff, M.D. (by invitation), New York Hospital-Cornell Medical

Center, New York, N. Y.

Balloon-kymographic studies of the normal human sigmoid colon have shown nearly continuous wave-like motility in all of a series of 300 subjects. Similar observations have been made upon fifty patients with non-specific ulcerative colitis, and in thirty-six tracings from twenty-six patients no phasic activity was present, the record approximating a straight line. This abnormality may disappear during remission of disease and reappear promptly when relapse occurs. It is unrelated to the extent

of bowel damage as estimated by x-ray and proctoscopy, and to fibrosis of the bowel wall. Wave-like contractions may reappear for short periods following administration of banthine, TEAC, urecholine and priscoline. Similar changes in sigmoid motility have been produced for short periods in normal subjects by the injection of acetylcholine or methacholine, and by unsympathetic interviews producing feelings of helplessness and defeat. It is concluded that this absence of wave-like activity in the sigmoid of patients with ulcerative colitis may represent sustained contraction resulting from neural impulses.

VALUE OF PNEUMOPERITONEUM EMPLOYED PRIOR TO SURGERY OF THE STOMACH AND SPLEEN. Bernard Maisel, M.D., Memorial Cancer Center, New York, N. Y.

Pneumoperitoneum induced in man and dogs two weeks prior to exploratory laparotomy produced a striking visceroptosis of the liver, spleen and stomach. As a result of this ptosis of the stomach there was a herniation of a long segment of esophagus from the mediastinum into the peritoneal cavity. This long intra-abdominal segment of esophagus markedly facilitated total gastrectomy and esophagojejunostomy performed through an abdominal incision. The ptosis of the spleen, from beneath the costal margin, since it provided infinitely better exposure of the vascular pedicle of the spleen aided significantly in its removal.

SERUM CHOLINESTERASE IN HEALTH AND DISEASE.

Louis J. Vorhaus, M.D. (by invitation), and
Robert M. Kark, M.D., University of Illinois
College of Medicine, Chicago, Ill.

<sup>4</sup> Serum cholinesterase is an enzyme or group of enzymes of hepatic origin about which little was known until recent years. Using Michel's electrometric method for the determination of its activity, extensive studies were made of its properties and alterations in health and disease. We have shown that in hepatic disease there is a characteristic depression of serum cholinesterase activity. Serial studies of its activity made in chronic and acute liver disease more closely reflected the changing status of hepatocellular function than any of ten commonly used liver function tests with which it was compared. Its activity is depressed in malnutrition and rises with rehabilitation. Low levels are also found in many types of anemias and these rise as the blood picture improves. Normal levels were found in patients ill with myasthenia gravis,

asthma, hyperthyroidism and hypertension. Exceedingly high levels were observed in patients ill with the nephrotic syndrome. Prolonged intravenous infusion of serum albumin caused a marked depression of serum cholinesterase activity. The data suggest that the serum cholinesterase molecule is synthesized in parallel with the albumin molecule, and that its synthesis is stimulated by factors which stimulate albumin production. Prompt and significant depression of serum cholinesterase activity has also been observed following administration of tetraethyl ammonium, vitamin K, folic acid and sodium amytal, probably due to reversible inhibition of the cholinesterase. Regeneration of serum cholinesterase following injection of di-isopropyl fluorophosphate has been studied, and the data suggest that the life span of the molecule is approximately four weeks.

A CORRELATION BETWEEN CHANGES IN SERUM PROTEIN FRACTIONS IN DIABETES MELLITUS. S. O. Waife, M.D., Michael G. Wohl, M.D. (by invitation) and Barbara Sigmond, M.D. (by invitation), Philadelphia General Hospital, Philadelphia, Pa.

When serum albumin levels fall, the serum globulin often rises. No quantitative expression of the relationship of these protein fraction changes is generally accepted. To study this problem statistical analyses were performed on 386 serum protein determinations (in duplicate) on 106 subjects (twenty-seven normal controls, twenty-eight hospitalized diabetic patients and fifty-one diabetics seen in the out-patient department). Albumin, globulin and gamma globulin concentrations were determined chemically. Significant differences (P < 0.1) were found in the mean value of total protein, albumin, globulin and gamma globulin fractions of the three groups. The hospitalized diabetics had a significantly lower albumin and higher globulin and gamma globulin levels than the controls. The clinic diabetics had intermediate values. Regression coefficients (of the diabetic values) show that the increase in gamma and total globulin does not proceed at a constant rate for each decrease in albumin. The rate is constantly diminishing. Plotting the A/G and A/GG ratios against albumin offers a more precise picture of the change and shows a correlation of +.87 and +.70, respectively. There was a +.87 correlation between total globulin and gamma globulin. The correlation between the absolute values of A:G and A:GG was -.42 and -.40, respectively. Equations enabling accurate estimations of ratio changes from actual levels are presented. As serum albumin levels fall in diabetes mellitus definite and predictable rises in serum globulin, chiefly the gamma globulin, fractions occur.

LIFE SITUATIONS, EMOTIONAL REACTIONS AND VARIATIONS IN URINARY EXCRETION OF 17-KETOSTEROIDS. Thomas H. Holmes, M.D., Loren D. Carlson, M.D., Robert B. Wilkins, M.D., Klarese Dorpat, M.D. and Theodore Dorpat, M.D. (introduced by Herbert S. Ripley, M.D.), University of Washington School of Medicine, Seattle, Wash.

Variations in urinary excretion of 17-ketosteroids observed in a variety of experimental situations appeared to be directly related to those integrated patterns of behavior which, because of past conditioning experiences, attitudes, motivation and aspirations, called for generalized mobilization of bodily resources for participation in action: In settings provocative of relative security and satisfaction, taking action was usually associated with a moderate decrease in excretion of 17-ketosteroids. In settings engendering competitive reactions or relatively intense feelings of anxiety, conflict, tension, or hostility, taking action was often associated with sustained or slightly elevated 17-ketosteroids excretion. If in such a setting action was not taken, marked elevations in excretion of 17-ketosteroids occurred, often of dramatic proportions. Exhausting action (heavy exercise) regardless of affect or life setting was invariably associated with a profound decrease in excretion of 17-ketosteroids followed by a marked rise during the recovery period. When because of depression, nonparticipation because of bodily discomfort or tranquility, taking action was not required and the ensuing inactivity was not accompanied by overt anxiety or conflict, tension or hostility, there was a decrease in excretion of 17-ketosteroids. To understand the variations in excretion of 17-ketosteroids observed to accompany different life situations, emotional reactions and patterns of behavior it is postulated that: (1) the alterations in the excretion of 17-ketosteroids observed were an index of the amount of adrenal cortical hormone produced; (2) during action tissue utilization of adrenocortical hormones occurs in skeletal muscles, is roughly proportional to the form, intensity and duration of the activity, and results in decreased excretion of 17-ketosteroids.

RELATION OF CUTANEOUS VASCULAR CHANGES, PAIN THRESHOLD AND ITCHING. David T. Graham, M.D., Helen Goodell, M.D., Harold G. Wolff, M.D. (by invitation), New York Hospital—Cornell Medical Center, New York, N. Y.

The relation of vascular changes in the skin to the pain thresholds of three normal subjects was studied. When arteriolar dilatation (indicated by rises in skin temperature) followed ingestion of nicotinic acid, injection of priscoline, or immersion of the legs in hot water, there was a significant lowering of pain threshold whether measured by thermal radiation or by pressure of a von Frey hair. No significant lowering of pain threshold occurred when the temperature of the small area of skin in which measurements were made was raised a similar amount by gentle heating with hot air, presumably avoiding vasodilatation. Changes in pain threshold (as measured by thermal radiation) may be related to differences in the intensity of radiation necessary to heat skin to a critical temperature. However, it must be inferred that the observed threshold changes during vasodilatation in the present experiments were in large part the consequence of some aspect of vasodilatation other than elevation of temperature. During vasodilatation and lowered pain threshold, itching was much more intensely aroused by light mechanical stimulation than during control periods. In view of the evidence that itch sensation results from weak stimulation of peripheral pain fibers, it is suggested that attacks of itching associated with vasodilatation in patients with skin disease result from lowering of the pain threshold so that previously unperceived stimuli are felt as itch.

RECURRENT THROMBOPHLEBITIS: A STUDY OF LIFE SITUATIONS, EMOTIONS AND THE CLOTTING TIME AND RELATIVE VISCOSITY OF WHOLE BLOOD. Robert A. Schneider, M.D., New York Hospital—Cornell Medical Center, New York, N. Y.

Thrombophlebitis is a disease of unknown etiology in which changes in the vessel wall, slowing of the blood stream and alterations in the physical characteristics of the blood have been implicated. Scant attention has been paid to the role of emotions and life situations in its pathogenesis. This study concerns a correlation of life situations and emotions with repeated measurements of clotting time and relative blood viscosity in six subjects with recurrent thrombophlebitis. Clotting time was measured

in siliconized tubes at 37°c. and the relative blood viscosity determined using a capillary pipette viscosimeter at 25°c. Three procedures were employed: (1) Life histories were correlated with initial and subsequent attacks of thrombophlebitis. (2) Day-to-day observations were made of the subjects' current life stress and the associated clotting time and blood viscosity values. (3) Stressful interviews were conducted and simultaneous measurements of the clotting time and blood viscosity made. Results were: (1) Past attacks of thrombophlebitis were found to have occurred in a setting of sustained anxiety and fear. (2) Weekly measurements over several months showed accelerated clotting time during periods of anxiety and fear. Two subjects developed thrombophlebitis while under observation, the attacks occurring during unusual stress associated with shortened clotting times. (3) Stressful interviews were productive of short clotting times when anxiety, fear and unexpressed anger could be elicited. This study suggests that sustained emotional stress productive of anxiety, fear and anger causes significant acceleration of blood coagulation and may play an important role, hitherto unappreciated, in the pathogenesis of thrombophlebitis. IMMUNOLOGIC HYPERREACTIVITY IN THE PATHO-

GENESIS OF RHEUMATIC FEVER AND OTHER DISEASES. Lowell A. Rantz, M.D., William P. Creger, M.D. (by invitation) and Sun Hak Choy, M.D. (by invitation), Stanford University School of Medicine, San Francisco, Calif.

Numerous investigators have shown that Group A hemolytic streptococcal respiratory infection complicated by rheumatic fever is associated with the production of larger amounts of various antistreptococcal antibodies than is the uncomplicated illness. One explanation of these observations is that immunologic hyperreactivity may be an essential characteristic of persons susceptible to the development of nonsuppurative streptococcal complications. Experiments were designed to test this hypothesis which included the stimulation of healthy human beings with the antigens of influenza A and B, and blood of heterologous group. Approximately 5 per cent of these persons reacted to such stimulation by the production of excessive amounts of all three antibodies, and no others produced comparable amounts of any one. A small group of rheumatic subjects and others suffering from diseases in which inappropriate immunologic reactions may play a

role were also tested by the red blood cell technic and all, except cases of rheumatoid arthritis, were found to be hyperreactors. This preliminary study indicates that such hyperreactivity may be an important factor in the pathogenesis of certain pathologic processes and emphasizes the possible role of immunologic mechanisms in their causation.

Pressure Volume Characteristics of the Lungs in Chronic Poliomyelitis Patients. J. E. Affeldt, M.D. (by invitation), J. L. Whittenberger, M.D. and B. G. Ferris, Jr., M.D. (by invitation), Harvard School of Public Health, Boston, Mass.

A study of the elastic characteristics of the chest and lungs has been made in patients with chronic poliomyelitis who have severe respiratory involvement. When lung volume change in terms of per cent of expected normal vital capacity is plotted against the pressure used in the body type respirator, a curve can be drawn indicating the degree of volume change per unit pressure change. The slope of the curve provides quantitative evidence for the long-held clinical impression concerning chest fixation. The pressure-volume characteristics have been correlated with the severity and duration of the disease and the changes in lung volume subdivisions. There is evidence which suggests that repeated observations would improve the pressure-volume characteristics because of the stretching of the chest produced in making the determinations. The pressure-volume curve could be used for fairly precise evaluation of the degree of fixation, of its rate of advancement or improvement and as an index of the effectiveness of specific therapeutic procedures.

EFFECT OF CYSTEINE ON NITROGEN MUSTARD THERAPY IN HUMANS. PRELIMINARY STUDY. Austin S. Weisberger, M.D., Robert W. Heinle, M.D. and Bennett Levine, M.D. (by invitation), Western Reserve University School of Medicine, Cleveland, Ohio.

Cysteine prevents the leukopenia induced by nitrogen mustard (HN<sub>2</sub>) in animals as well as protecting against the lethal effects of irradiation. The effect of cysteine on HN<sub>2</sub> therapy was studied in ten patients. Fifteen to thirty gm. of cysteine were administered intravenously prior to two daily doses of 0.2 to 0.4 mg. of HN<sub>2</sub> per kg. Definite protection against leukopenia as well as a marked reduction in the nausea and vomiting usually occurred. Although some leukopenia occurred occasionally, it was not as

severe as would have been expected without cysteine. The average fall in total leukocyte count was 58 per cent and the average fall in neutrophils was 54 per cent of control counts. In two patients almost complete disappearance of leukemic cells with relatively little change in neutrophils occurred. In general, the protective effect of cysteine on HN2 induced leukopenia in humans was not as marked nor as consistent as in animals. This may be due to involvement of bone marrow with disease, differences in cysteine-HN<sub>2</sub> dose ratio, or to species differences. A protective effect occurred, however, which was often striking, without any noticeable loss of HN<sub>2</sub> effect on the disease. It is suggested that the action of cysteine in preventing leukopenia may be due to a specific protective effect on leukocytes rather than to chemical inactivation of HN2. This technic permits use of larger doses of HNo.

ENERGY EXPENDITURE STUDIES IN THE CARDIAC PATIENT AS A BASIS FOR REHABILITATION. Joseph G. Benton, M.D., Henry Brown, M.D. (by invitation) and Howard A. Rusk, M.D. (by invitation), New York University—Bellevue Medical Center, New York, N. Y.

Oxygen consumption as a measure of energy cost was determined by means of closed system respirometry in a group of twenty-six normal subjects and compared with data similarly derived from a group of sixteen compensated cardiac patients. The latter included all etiologic varieties of heart disease and all were on adequate cardiac maintenance regimens. Functional and therapeutic classifications ranged from I A to III C. Skeletal-motor, pulmonary disease and thyroid and hematologic dyscrasias precluded selection for study in both groups. Ambulation activities on level ground and stair walking were chosen as initial work loads for analysis. These were of graduated intensity and were performed under standardized conditions with regard to duration and speed. Oxygen consumption was computed in milliliters per kilogram of body weight. Preliminary data indicate that under the conditions studied, the compensated cardiac patient expends no more energy as measured by oxygen consumption, provided cardiac reserve is not exceeded, than does the normal individual.

A SIMPLIFIED BEDSIDE PROTHROMBIN TEST. Victor G. de Wolfe, M.D., Abbott A. Newman, M.D. (by invitation) and Irving S. Wright, M.D., Cleveland Clinic, Cleveland, Ohio.

Quick in 1939 stated that the clotting time of

blood or plasma is a quantitative measure of prothrombin concentration, provided an excess of thromboplastin and a constant concentration of calcium are present. Tests of prothrombin time are done on plasma and are involved and time-consuming. Simplified prothrombin tests performed on whole blood have been described by Ziffren et al. (1939) and others. More recently Barnard (1949), Schwager and Jacques (1949) and Lewis et al. (1950) have described simplified methods performed on whole blood in dicumarolized patients. These tests have apparently yielded reliable results. We have used a modification of the method of Ziffren et al., using whole blood and an excess of a commercial thromboplastin on dicumarolized patients. The study was divided into two parts. In Part I, 150 determinations were done on ten patients hospitalized for various thromboembolic diseases. Prothrombin times were performed on the same sample of blood used for the simplified tests. A fairly close correlation was obtained between the simplified test and the prothrombin time done by the Link-Shapiro method. In Part II, refinements in technic were instituted and 248 determinations were done on fourteen additional patients on dicumarol. A much closer correlation was obtained between the simplified test and the Link-Shapiro prothrombin time. We believe that this simplified test, which can be performed at the bedside, is an accurate estimation of the blood prothrombin concentration and that patients receiving dicumarol therapy can be controlled adequately with this test alone. EFFECT OF TERRAMYCIN UPON E. COLI BACTERIO-

PHAGES. Michele Gerundo, M.D. and Guydell L. Schwartz, M.D. (by invitation), Creighton Uni-

versity Medical School, Omaha, Neb.

Terramycin was tested against phages T<sub>4</sub>, T<sub>7</sub> and T<sub>6r+</sub>, which are known to be active against E. coli bacteriophages. A 1:2000 solution of terramycin in sterile saline was added in increasing amounts to tubes inoculated with E. coli and E. coli plus each of phages  $T_4$ ,  $T_7$ , and  $T_{6r+}$ . E. coli was completely inhibited by 1/2 of a cc. of terramycin solution, but grew well in tubes containing  $\frac{1}{10}$  of a cc. of the solution. At this last concentration, however, it was completely inhibited when one of the phages was added to the tubes. To test whether terramycin had destroyed the phages,  $\frac{1}{2}$  of a cc. from these tubes were transferred to fresh tubes inoculated with E. coli bacteriophages. The terramycin-treated phages showed the same lytic activity as the

untreated controls and were successfully transplanted in serial subcultures. In rechecking the experiments by using ten times the minimal amount of terramycin necessary to inhibit growth of a E. coli in conjunction with phage, the phages were again successfully recovered from the broth even after one week contact with the antibiotic. Under phase contrast microscope the particles of phage were clearly seen attached to the bacteria as in the controls. From the experiments it is concluded that terramycin is effective against E. coli, that it may have synergistic action with phage, but it is without effect upon phage. It cannot be stated whether ineffectiveness extends also to other viruses.

HEMATOLOGIC PROBLEMS IN DISSEMINATED LUPUS ERYTHEMATOSUS. Edmund L. Dubois, M.D. (introduced by Robert R. Commons, M.D.), University of Southern California School of Medicine, and Los Angeles County Hospital, Los Angeles, Calif.

Early diagnosis of lupus is often dependent on exhibition of the Hargraves phenomenon by the leukocytes. The importance of this test is emphasized by our series of patients with primary hematologic diagnoses who subsequently were shown to have lupus as the underlying disorder. The hematologic diseases are acquired hemolytic anemia with positive Coombs test, thrombocytopenic purpura and leukopenia. These findings are consistent with the syndrome described as caused by "hypersplenism." The hematopoietic marrow of lupus patients is similar to that of patients with "hypersplenism." NATURAL HISTORY OF HYPERTENSION WITH

Papilledema. Mary F. Schottstaedt, M.D. and Maurice Sokolow, M.D., University of California, San Francisco, Calif.

As part of a long-range study of the natural history of hypertension, a survey was made of all cases of hypertension associated with papilledema (malignant hypertension) seen in the past ten years. One hundred four cases were included; follow-up information was obtained in all. The average survival after the discovery of papilledema was thirteen months in patients with good renal function and four months in those with impaired renal function. Autopsies were performed in thirty-three cases and demonstrated that nephrosclerosis was the most likely lesion when good renal function was retained in the presence of hypertension and papilledema.

Study of our cases showed that no patients in whom papilledema persisted survived more than thirty months. Of the total of thirteen patients who showed disappearance of papilledema, eight survived more than thirty months and but one died of clinical renal insufficiency in contrast to the usual course. The effect of treatment is indicated by the fact that of eighty-eight untreated patients, only two showed spontaneous reversal of papilledema, whereas of sixteen treated patients (seven sympathectomy, eight low sodium diets, one nephrectomy), eleven showed reversal of papilledema. It is believed that disappearance of papilledema implies a decrease in the tempo of malignant hypertension and that an increased survival rate may be expected, provided vascular damage has not been too extensive. Since treatment in the presence of renal impairment is of no avail, early diagnosis and prompt, vigorous treatment are essential in malignant hypertension before renal impairment has developed and before irreparable damage to cardiac musculature and cerebral vessels has occurred.

Pulmonary Leukocyte Removal Mechanism in Leukemic and Non-leukemic Patients. Howard R. Bierman, M.D., Keith H. Kelly, M.D. (by invitation), Nicholas L. Petrakis, M.D. (by invitation) and Frederick W. King, M.D. (by invitation), University of California School of Medicine, San Francisco, Calif.

The intravenous administration of 0.1 to 0.3 mg, of histamine is followed by marked leukopenia. By catheterization of the right ventricle and aorta or cannulation of major arteries it has been possible to show in fourteen non-leukemic patients that the leukopenia is due to a transient removal of white blood cells within the pulmonary circulation. By similarly sampling arterial and venous sites, it was also possible to show an arterial leukopenia during the Valsalva maneuver in twelve non-leukemic patients. Comparable studies on seven patients with lymphatic leukemia or lymphosarcoma with lymphocytes predominant in the bone marrow failed to reveal this mechanism of leukocyte removal by the Valsalva maneuver. The administration of up to 0.9 mg. of histamine intravenously within thirty seconds also failed to induce the lung mechanism to remove leukocytes.

## Case Report

## Charcot Spine Due to Diabetic Neuropathy\*

GARY ZUCKER, M.D. and MAXWELL J. MARDER, M.D.

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described in a variety of neurologic disorders, e.g., tabes dorsalis, syringomyelia, leprosy and peripheral nerve injuries. Its occurrence as a component of diabetic neuropathy was first noted by Jordon¹ in 1936. He cited the case of an elderly diabetic patient with an advanced neuropathy and foot drop. Over a period of two years she had developed a Charcot ankle. In addition she had destructive lesions in the bones of the feet due to an unusual type of chronic osteomyelitis.

In 1942 Bailey and Root<sup>2</sup> made brief reference to two cases with Charcot changes occurring in the feet. Jordon<sup>3</sup> in 1943 recorded three additional instances in a paper discussing the effects of diabetes on the nervous system. A critical examination of the histories suggests that two patients (Cases I and III) may not have had true neuropathic joints. The first had destructive bone changes in the foot underlying an infected ulceration of the soft tissue. Such apparently neuropathic bone lesions have been discussed in great detail recently by Hodgson, Pugh and Young.4 They reviewed x-ray films of sixty-one cases in which a radiographic diagnosis of neuropathic bone changes had been made. All cases had chronic soft tissue infection with ulceration adjacent to the involved bones. Only a few had evidences of nervous system involvement. They concluded that these bone changes were due to a type of osteomyelitis secondary to chronic infection of the contiguous soft tissues. The third patient presented by Jordon had a localized destructive lesion of the adjacent areas of the bodies of the fourth and fifth lumbar vertebrae. The diagnosis was thought to be some type of infectious lesion of the spine and not a Charcot spine. It would appear, then, that of the three cases reported by Jordon only one was an unquestionable Charcot joint. This one occurred in the foot.

By 1947 Bailey and Root<sup>5</sup> were able to collect seventeen such cases of 20,000 diabetics treated in their clinic. The joint changes were observed only in the tarsus and metatarsus. The earliest gross changes consisted of unilateral or bilateral thickening of the tarsal region without the presence of fluid, pain, redness or heat. When the lesion was fully developed, there was eversion and external rotation of the foot and flattening of the longitudinal arch. The changes seen on x-ray were similar to those in Charcot joints of syphilis with the following exceptions: (1) the involvement was limited chiefly to the tarsus and the proximal end of the metatarsal bones; (2) there was no new bone formation and (3) there was absence of sclerosis in adjacent bones. They considered the exclusive localization in the tarsus and metatarsus as characteristic for diabetic neuropathy. Although the foot seems to be the site of predilection, several reports indicate that other joints in the lower extremity may be attacked as well. In 1945 de Takats<sup>6</sup> described Charcot ankles and knee in a twentyeight year old male with diabetes of fifteen years' duration and diabetic pseudotabes. Also, in 1947 Foster and Bassett<sup>7</sup> presented two cases in one of whom the ankle as well as the tarsus and metatarsus was involved. Shore8 and Spear9 each described a case with knee involvement.

The purpose of this article is to demonstrate the occurrence of a typical Charcot spine in a diabetic with severe pseudotabes. This case is of special interest because it appears to be the first Charcot spine to be reported as a result of diabetic neuropathy and because the etiologic and pathologic nature of the lesion was fully corroborated by a complete autopsy examination. Although other destructive lesions of the spine have been described in diabetics, some of them have been pathologic fractures<sup>10,11</sup> and others infectious in nature.<sup>3</sup>

#### CASE REPORT

A. G., a forty-seven year old Jewish housewife, was first admitted to Beth Israel Hospital on January 27, 1948, complaining of swelling of the

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ankles and eyelids of five days' duration and increasing dyspnea and dry cough.

Diabetes was diagnosed in 1934. Between 1936 and 1946 she had six hospital admissions for diabetic acidosis and four for insulin shock. Between admissions there was poor regulation of her diabetes in spite of the use of insulin. In 1945 she became dizzy and fell on her back in the bathroom. X-ray films of the spine revealed no fracture. Since that time she had back pains and limitation of flexion of the spine. In August, 1946, a radiographic diagnosis of osteoarthritis was made. In October, 1947, she was given a brace for her back.

Her family history was non-contributory. Her husband was living and well and she had three healthy children.

Physical examination revealed the temperature was 99°F., pulse rate 96, respirations 28, blood pressure 172/110, the patient was dyspneic, slightly cyanotic and pallid. Eyelids were edematous. External ocular movements were normal. The pupils were small, slightly irregular, equal in size and reacted to accommodation but not to light. Optic discs were normal. Minimal A-V compression and old waxy spots were seen in both fundi. A fresh, small hemorrhage was present in the right fundus. The tongue was smooth, moist and reddened. The neck veins were markedly distended. Medium moist rales and dullness were present at both lung bases. The apex beat could not be felt. The heart sounds were distant and had a tic-tac quality at the apex. The rhythm was regular. A2 equalled P<sub>2</sub>. Liver dullness percussed three fingerbreadths below the costal margin. One plus ankle edema was present. The dorsalis pedis pulses were palpable bilaterally. Moderate thoracic kyphosis was noted. There was a posterior knuckling of the lumbar spine. This area was slightly tender. The knee jerks were hypoactive. Ankle jerks were absent. There was complete loss of vibration and position sense below the knees. The Romberg was positive, as were the Westphal and Abadi signs. No Babinski was elicited.

The laboratory findings were as follows: Urinalysis showed a specific gravity from 1.004 to 1.016, albumin 1 to 2 plus, glucose 0 to 4 plus, acetone negative, 1 to 2 red blood cells and up to 10 white blood cells per high power field. There were 3,030,000 red blood cells, hemoglobin 8.5 gm., white blood cells 8,500, polymorphonuclears 47 per cent, staffs 3 per cent, lymphocytes 28 per cent, eosinophils

10 per cent, monocytes 12 per cent. Erythrocyte sedimentation rate (Westergren) was 80 mm. in one hour. Fasting blood sugar was 127 mg. per cent to 411 mg. per cent, non-protein nitrogen 65 mg. per cent, total proteins 6.0 gm. per cent with albumin 2.6 gm. per cent and globulin 3.4 gm. per cent, cholesterol 250 mg. per cent, cholesterol esters 193 mg. per cent, CO<sub>2</sub> content 46.7 volumes per cent, calcium 10.9 mg. per cent, phosphorus 3.5 mg. per cent, alkaline phosphatase 2.7 Bodansky units. Wassermann, Kahn and Kline tests were negative.

On admission the patient was considered to have congestive heart failure due to hypertensive and arteriosclerotic heart disease. She improved satisfactorily with digitalis, oxygen, mercurial diuretics, salt restriction and bed rest.

The diabetes was difficult to control. She excreted between 5 and 55 gm. of glucose daily. Yet on the eleventh day, while taking only 35 units of protamine zinc insulin, she was found in insulin shock. At other times she had acetonuria in spite of supplements of regular insulin.

The impairment of renal function, the azotemia, persistent albuminuria, hypoalbuminemia and the hypertension led to suspicion of intercapillary glomerulosclerosis.

Radiographic examination of the lumbar spine disclosed extensive destruction and disorganization of the second, third and fourth lumbar vertebrae. (Fig. 1.) The third lumbar vertebra was almost completely disintegrated. There was considerable bone production within the area of the destroyed vertebrae. No sclerosis was seen in the adjacent uninvolved bodies. The x-ray appearance was that of a Charcot or neuropathic spine.

A spinal tap revealed normal pressure and manometrics; total protein 93.7 mg. per cent, glucose 305 mg. per cent, chlorides 693 mg. per cent, no cells, colloidal gold negative, Wassermann negative.

Cystometric studies revealed a hypotonic bladder.

Skin temperatures of the feet were normal.

The patient was readmitted on June 15, 1948, because of painful swelling and redness of the right ankle and leg of two days' duration. Walking was difficult but she had remained ambulatory.

Physical examination revealed the significant changes in physical findings were those confined to the right lower extremity and the nervous system. There was marked swelling and redness

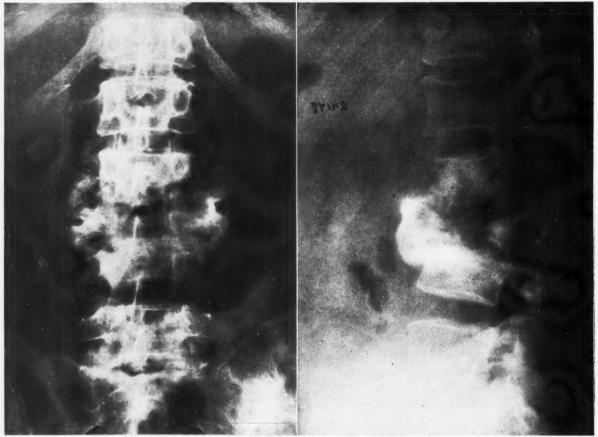


Fig. 1. Charcot spine involving L2, 3 and 4. Note almost complete destruction of L3 and the new bone formation in this area. There is no sclerosis in L1 or 5.

with but slight tenderness about the right ankle. The ankle joint was completely disorganized. Passive motion in all directions elicited unusual bony crepitus but no pain or spasm. The neurologic signs had progressed. Vibratory sense was absent below the lower dorsal spine and diminished in the hands; position sense was poor in the feet; light touch was diminished in the lower extremities. All deep reflexes were absent except for the right biceps jerk. The pupils were equal, irregular and measured 2 mm. in diameter. They reacted to accommodation but not to light. A sweat test showed absent sweating below the mid-thighs and diminished sweating over the entire abdomen and the left hemithorax anteriorly and posteriorly.

X-ray of the right ankle showed a fracture of the lower end of the tibia and fibula with slight medial displacement of the tibial fragment. No osteoporosis of the tibia was seen but there was slight osteoporosis of the phalanges. Some of the interosseous arteries showed calcific changes.

It was apparent that the patient had sustained a pathologic fracture in an anesthetic limb. The fracture was first treated with a plaster cast up to the knee. On the fifteenth hospital day a Kirschner pin was inserted through the os calcis.

During the fourth week in the hospital the patient developed a greatly distended atonic bladder with a residual urine of 2,400 cc. The next day she revealed signs of cerebral hemorrhage and died on the thirthieth day in the hospital.

The autopsy findings were as follows: Examination of the vertebrae upon opening the abdomen showed an irregular bony mass was palpated from L1 to L5. The mass had its greatest width from L2 to L4 where it measured 8.5 cm. across and protruded 3 cm. above the adjacent bodies. On coronal section there was moderate lipping of the lower thoracic and lumbar vertebral bodies. The bodies of L2, 3 and 4 were compressed with almost complete obliteration of L3. The associated intervertebral discs were completely destroyed. The central portion of L3 was 1 cm. thick and replaced by fibrous strands in its remaining marrow. The lateral portions of L3 flared out and here the

bony fibrous mass reached a height of 2.5 cm. L2 was slightly compressed and its inferior portion was involved by fibrous tissue. L4 was similarly compressed and its superior surface was destroyed and replaced by fibrous tissue. Slight increase of fibrous tissue was noted in the lowermost portion of L1 and the uppermost portion of L5.

In the right leg and ankle there was extensive subcutaneous hemorrhage over the right tibia and fibula from the mid-portion to the ankle. On coronal section through the tibia hemorrhagic areas were seen scattered throughout the yellow marrow. A fracture at the junction of the medial condyle of the tibia and the shaft extended upward 1.8 cm. to a point 1 cm. from the medial aspect of the tibia. The cartilage of the anterior two-thirds of the trochlear surface of the talus was extremely thin and smooth. On the posterior one-third of this surface the cartilage was absent and an eburnated bony surface was seen. The right tibial nerve was removed.

Examination of the brain showed there was minimal sclerosis in the circle of Willis. Some cortical atrophy in the frontal lobes was present. A small subarachnoid hemorrhage was seen in the right frontal lobe between the first and second convolutions. There was some increase in the size of the anterior horns. No lesion was visible in the upper mid-brain. The meninges appeared normal.

The dura of the spinal cord appeared to be normal. There was no thickening of the arachnoid. The spinal cord in the thoracic region appeared to be somewhat smaller and slightly browner than average.

The endothelial surface of the ascending aorta was yellow. No treebark wrinkling was noted. The aorta was moderately atherosclerotic but fairly elastic.

Microscopically, section of the vertebrae through the compressed portions of the bodies of L2 and L3 showed marked fibrous replacement of the marrow spaces. The bony lamellas were thick and contained numerous basophilic striations indicative of bone deposition. Between the two bodies there was a zone of rather fibrous granulation tissue containing numerous newly formed capillaries, small lymphocytes and plasma cells. Considerable new bone formation was discernible in this area. Section through the body of L1 showed normal trabeculas without evidence of either decalcification or osteosclerosis. Hematopoesis was moderately active. There

was no fibrous replacement of the marrow spaces. A rather tortuous artery showed arteriosclerotic thickening of its wall. The cartilage layer at the intervertebral joint appeared thin and was overlaid by a thick amorphous zone in which ghosts of cartilage cells could be made out.

Section of the tibia through the fracture line showed a fibrous callus in which new bone formation was taking place. The periosteum was thickened at the site of the new bone formation.

Microscopic examination of the aorta revealed there was moderate atheromatosis. No changes of syphilis were seen in the media.

In the kidneys arteriolarsclerosis and intercapillary glomerulosclerosis (Kimmelsteil-Wilson lesion) were present. Some lipid was seen in the glomeruli and in the tubular epithelium.

In the tibial nerve extensive degeneration of the myelin sheaths was present. (Figs. 2A and B.) The nerve bundles were shrunken and scalloped. The spaces between the nerve bundles were increased. There was marked proliferation of collagenous tissue in the perineureum and endoneurium. A medium-sized artery showed marked thickening of its wall. Similar changes were seen in the smaller arteries, some of which were almost entirely occluded by medial hypertrophy.

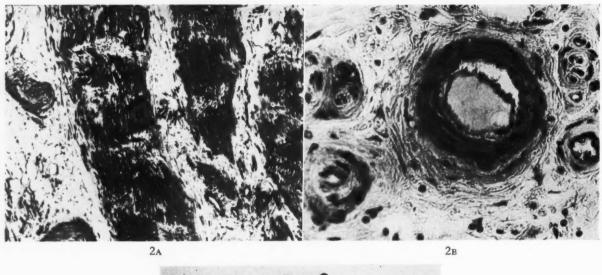
In the lumbar posterior root there was marked thickening of the media of the mediumsized arteries and some degeneration of the myelin sheaths.

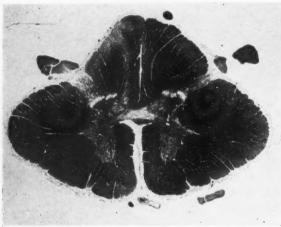
The cauda equina showed the media of the small and medium-sized arteries was distinctly thickened. Myelin sheaths stained poorly but were not disintegrated.

The sacral cord showed there was some thickening of the pia. The arterioles throughout the spinal cord were slightly thickened. There was slight demyelinization of the fasciculus gracilis. The anterior horn cells were degenerated as evidenced by vacuole formation, increase in pigment and some chromatolysis.

Examination of the lumbar cord revealed there was patchy, asymmetrical degeneration of the myelinated fibers in the fasciculus gracilis. A similar but lesser change was also seen in the fasciculus cuneatus on one side. (Fig. 2c.)

The thoracic cord revealed similar asymmetrical demyelinization as described in the lumbar cord. Only a few cells remained in the lateral horns and these showed chromatolysis.





2c

Fig. 2. A, Myelin stain of the tibial nerve showing demyelinization, atrophy of nerve bundles and proliferation of collagen; B, thickening of the walls of small and medium-sized arteries in the tibial nerve; C, lumbar cord showing patchy and asymmetrical demyelinization in the posterior columns.

The cervical cord showed similar but slightly more marked demyelinization.

Neuropathologic diagnosis was as follows: The appearance of the degeneration in the spinal cord, particularly its patchy and asymmetrical distribution in the posterior columns, is quite unlike the picture of tabes dorsalis. These changes are entirely compatible with the arteriosclerotic lesions associated with diabetes. The parenchymatous degeneration in the peripheral nerve is of the type seen with arteriosclerotic involvement of the vasa nervorum.

#### COMMENT

The clinical evidences of diabetic neuropathy in this patient were quite impressive. They included absent deep reflexes, impaired vibratory and position sensation, diminished cutaneous sensation, Argyll Robertson pupils, diminished

to absent sweating in the lower half of the body and impaired innervation of the urinary bladder. This syndrome has long been referred to as diabetic pseudotabes. However, the coexistence of a Charcot spine at first raised the question as to whether this patient might have serologically negative tertiary syphilis with tabes dorsalis. The same uncertainty in the differential diagnosis was stressed by Jordon<sup>1</sup> when he was confronted by his original case with a Charcot ankle and by Spear9 when he encountered a Charcot knee. On clinical grounds alone it was even more difficult to accept a Charcot spine as a complication of diabetic neuropathy. In the past most of them have been caused by syphilis and syringomyelia. The negative family history and negative blood and spinal fluid serology did not preclude the diagnosis of syphilis. Charcot joints have been described by Key<sup>12</sup> and others

in luetics who gave no history of infection and who had negative serologic tests. The only positive findings in these cases were other clinical evidences of syphilis, e.g., Argyll Robertson pupils. Similar pupillary changes were present in our case. In the absence of a complete pathologic examination of the central and peripheral nervous systems it would have been difficult to eliminate syphilis as the etiologic factor in the production of the Charcot spine reported here.

The histologic studies established beyond question that this patient did not have tabes dorsalis but did suffer from an advanced degree of diabetic neuropathy. The changes seen in the peripheral nerves and the spinal cord were similar to those described by Woltman and Wilder<sup>13</sup> as being typical for diabetes. In the peripheral nerves these consisted of patchy demyelinization of nerve fibers, atrophy of nerve bundles with fibrous tissue replacement and thickening of the walls of the small and mediumsized vasa nervorum. (Fig. 2A and B.) The changes in the spinal cord were confined mostly to the posterior columns and particularly to the fasciculus gracilis. Here there was slight, patchy and asymmetrical demyelinization (Fig. 2c) which was quite unlike the changes seen in tabes dorsalis. The latter condition is characterized by intense, confluent and symmetrical atrophy of the posterior columns; perivascular infiltration of lymphocytes; degeneration of the dorsal roots at the point of penetration of the arachnoid and lymphocytic infiltration of the leptomeninges and dura with ultimate fibrosis. 14 None of these histologic abnormalities were seen in any sections of the cord in our case. Moreover, careful gross and microscopic examination of all the other organs of the body failed to uncover any pathologic lesions of syphilis.

The unique localization of the Charcot joint in the lumbar spine was probably attributable to the severe back injury sustained about two and one-half years before the diagnosis of neuropathic joint was made. It is now generally agreed that Charcot joints result from a combination of trauma and loss of deep joint sensibility. Foster and Bassett<sup>7</sup> in their excellent discussion of this subject enumerated the following factors as being instrumental in the causation of a Charcot joint: (1) trauma from repeated small injuries, continued movement of a diseased limb or an isolated major trauma; (2) intact motor power to the affected joint;

(3) impairment of afferent pain impulses; (4) diminution or absence of afferent proprioceptive impulses which normally inhibit hypermotility of joints; (5) chronicity of the underlying nervous disorder and (6) metabolic disturbances conditioned by hypotonic arteries and a defective temperature-regulating mechanism.

The exact onset of the Charcot spine is not known but it was not present immediately after the accident when she fell on her back in 1945. That some changes were taking place and some injury had resulted can be deduced from the continual pain subsequent to this fall. Minor bony changes were present in 1946 warranting a diagnosis of osteoarthritis. It is possible that these may have been early neuropathic joint changes. Lipping of the vertebral bodies and eburnation of the subcortical bone have been described as the earliest radiographic changes in Charcot spine. In any case fully developed destructive changes were visualized radiographically by January, 1948, at the time of her first admission.

The Charcot feet described by Bailey and Root<sup>5</sup> were characterized by rapid development, absence of pain and no evidence of new bone formation in the area or sclerosis in the adjacent bones. However, most of the other reports3,6,7,9 do mention pain and new bone formation in the foot, ankle and knee lesions. Our case was characterized by slow development over a period of two and one-half years and by constant but mild pain. Radiographically, there was new bone formation in the destroyed area but no sclerosis in the adjacent bones. The latter characteristic should help distinguish diabetic Charcot spine from that seen in syphilis where sclerosis in adjacent bones is a prominent feature.

Treatment of these neuropathic joints has not been very satisfactory. Bailey and Root<sup>5</sup> stated that no effective therapy was available. Amputation had to be carried out in a few. DeTakats<sup>6</sup> removed fragments from a knee joint on two occasions to relieve locking and swelling. He also suggested that arthrodesis might be indicated occasionally for a flail joint. Parsons and Norton<sup>15</sup> reported arrest of destructive changes in the feet of two patients followed up forty-seven and twenty-eight months after lumbar sympathectomy. Both cases had chronic infection and circulatory insufficiency in the feet. The bone changes may have been secondary to the overlying soft tissue infection as emphasized

by Hodgson, Pugh and Young.4 If so, the arrest of the bone destruction may have followed improvement in the circulation and the clearing of the infection.

#### SUMMARY

A case of Charcot spine due to diabetic neuropathy is described. The diabetic etiology was substantiated by complete pathologic examination. This appears to be the first such case recorded in the literature.

Acknowledgment: We are indebted to Dr. Lewis D. Stevenson for his aid in making and examining the neuropathologic sections.

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# Diabetogenic Effect of Cortisone and ACTH in a Non-diabetic Patient with Rheumatoid Arthritis\*

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The diabetogenic effects of cortisone or adrenocorticotropic hormone (ACTH) have been attributed to diminished carbohydrate utilization, increased carbohydrate production due to augmented gluconeogenesis, insulin antagonism or damage to pancreatic islet cells or diminished blood glutathione levels. Increased renal clearance of glucose due to increased glomerular filtration rate or reduced tubular reabsorption may also contribute to glycosuria.

Diabetes has been induced in the experimental animal first by administration of extracts, either from the anterior pituitary or the adrenal cortex, and later by injecting normal rats with cortisone, compound B (corticosterone), compound F (17-hydroxycorticosterone) or ACTH. (Table 1.) It has been demonstrated that extracts of the adrenal cortex or the anterior pituitary gland depress utilization of carbohydrate and promote deposition of glycogen; the former affect principally the concentration of liver glycogen and the latter, muscle glycogen. 19 Normal mice become insulin resistant when injected with cortisone, compound B, compound F or ACTH.20 In normal human volunteers ACTH produces reversible diabetes and an increased resistance to insulin. 15 In patients with Addison's disease cortisone corrects the defect in carbohydrate metabolism which desoxycorticosterone acetate (DCA) alone does not. In patients with diabetes mellitus cortisone intensifies the diabetes and increases resistance to insulin. 16-18

The occurrence of diabetes mellitus or significant diminution in carbohydrate tolerance in non-diabetic patients treated with cortisone or ACTH is not common. In none of the thirty-three patients reported by Sprague and his associates<sup>21</sup> were more than traces of sugar observed in the urine nor were there significant changes in the mean values of the blood sugar concentration. In a report by Baehr and his associates<sup>18</sup> severe diabetes developed in one of fourteen patients with disseminated lupus erythematosus when treated with ACTH. This patient had a normal glucose concentration in the blood before treatment but presented a strong family history of diabetes.

The case of juvenile rheumatoid arthritis (Still's disease) reported in this paper demonstrates an unusual and severe effect on carbohydrate metabolism by cortisone and ACTH. There was no history of diabetes in the immediate family or in the maternal or paternal relatives. A glucose tolerance test performed before administration of cortisone was normal. The induced diabetes remained reversible, yielded to insulin and did not interfere with an excellent clinical response. The time required to restore the glucose tolerance to normal was longer with each successive course. As the total amount of hormone given was increased and the period of administration prolonged, glycosuria persisted for longer periods after the discontinuance of cortisone. When cortisone was administered in single doses of 50 mg. every 48 hours, marked clinical improvement of the arthritis was maintained, weight continued to increase, fasting blood sugar was only moderately elevated, carbohydrate tolerance was impaired to a lesser degree than when the patient received daily doses of 80 mg. and glycosuria disappeared. Adrenocortical function, as

<sup>\*</sup> From the Department of Medicine, and the Study Group on Rheumatic Diseases of New York University College of Medicine, and the Children's Medical Service of Bellevue Hospital, New York, N. Y. The Study Group on Rheumatic Diseases is supported by a grant from the Masonic Foundation for Medical Research and Human Welfare.

tested by the eosinopenic response to ACTH, was unimpaired after one year's treatment.

#### CASE REPORT

V. M., a ten year old white girl, was apparently well until December, 1948. At this time,

on January 4, 1949. On admission both knees were swollen, warm, tender and limited in motion. A soft apical systolic murmur was heard again. The polyarthritis progressed to involve the small joints of the hands, wrists, elbows, shoulders and hips. Temperature fluctuated

Table 1

REPORTED EFFECTS OF ANTERIOR PITUITARY AND ADRENOCORTICAL HORMONES ON CARBOHYDRATE

METABOLISM IN EXPERIMENTAL ANIMALS AND HUMANS

Authors	Subjects	Hormone Used	Results						
Johns et al. <sup>5</sup>	Normal dogs	A.P.E. (fresh)	Hyperglycemia and glycosuria						
	Toads (HYPX and PANX)	Ant. Pit. (subcutane- ous implants)	Protection from toxic effect of insulin						
Britton et al <sup>7</sup>	Normal cats, rats, rabbits	A.C.E.	Hyperglycemia; increased glycogen in muscle and liver						
Evans <sup>8</sup>	Normal dogs	A.P.E. (alkaline)	Hyperglycemia, glycosuria and dimin- ished glucose tolerance						
Young <sup>9</sup>	Normal dogs	A.P.E.	Permanent diabetes						
Long <sup>3</sup>		A.C.E.	Hyperglycemia						
	Normal rat (liver slices)	A.C.E.	Glycogenolysis inhibited						
Thorn et al. <sup>11</sup>		A.C.E., Cpd. B or E	Defect in carbohydrate metabolism cor- rected						
Ingle <sup>1</sup>	Normal rats	Cpd. E	Hyperglycemia and glycosuria						
Ingle et al. 12	Normal rats	Cpd. B, F	Hyperglycemia and glycosuria (more for "F" than for "B")						
Ingle et al. <sup>13</sup>	Normal rats	ACTH	Hyperglycemia and glycosuria						
Sprague et al. 14	Addison's disease	Cpd. E	Glycosuria and ketosis when insuling withdrawn						
Conn et al. 15	Humans (normal)	ACTH	Hyperglycemia and glycosuria						
	Patients with diabetes and hypertension	Cpd. E	CHOH tolerance decreased; glycosuria						
Boland et al. <sup>17</sup>	Patients with diabetes and rheumatoid arthritis	Cpd. E	Insulin resistance						
Baehr et al. <sup>18</sup>	Patients with lupus erythe- matosus	ACTH	Severe diabetes induced						
Kass et al.26	Patient with pneumonia	ACTH	Renal glycosuria						

HYPX = Hypophysectomized

PANX = Pancreatectomized

A.P.E. = Anterior pituitary extract

A.C.E. = Adrenocortical extract

Cpd. E = 17-hydroxy-11-dehydrocorticosterone (cortisone)

Cpd. F = 17-hydroxy corticosterone

Cpd. B = Corticosterone

ACTH = Adrenocorticotropic hormone

several days after a brief illness of sore throat and coryza, she complained of pain in the right knee joint but was able to walk with a slight limp. Within two weeks, fever of 102°F, and redness and swelling of the interphalangeal joints of both hands were noted. These findings together with an apical murmur, anemia and an elevated erythrocyte sedimentation rate led to a diagnosis of rheumatic fever and the administration of salicylates. Nausea and vomiting which had been mild before therapy became severe and the patient was unable to tolerate salicylates even when administered by rectum.

The patient was admitted to Flushing Hospital

sharply between normal and 105°F. Throughout the hospital stay the patient's white blood count ranged between 4,500 and 10,000 with about 50 per cent polymorphonuclear leukocytes. On admission the red blood count was 3.5 million and the hemoglobin concentration was 8.7 gm. per cent. After three transfusions of approximately 250 cc. of whole blood each the red blood count increased to 5 million and the hemoglobin to 12 gm. The erythrocyte sedimentation rate remained elevated. Repeated urinalyses were negative. The tuberculin test was positive. Electrocardiograms demonstrated a sinus tachycardia and a slightly prolonged

(.20 second) P-R interval. A bone marrow aspiration was reported to be normal. Roent-genograms of the chest, skull, pelvis, spine and long bones were negative. Three blood cultures were sterile and agglutinations for typhoid, paratyphoid, Brucella abortus and Proteus OX19 were negative.

Penicillin, streptomycin and sulfonamides were administered without effect and the patient became progressively worse. Musculoskeletal pain was so marked that she could not be turned in bed without discomfort. Weakness and debilitation became severe and the patient who had weighed 72 pounds before illness lost 30 pounds in seven months. She was discharged from that hospital unimproved on March 3, 1949.

At home she was confined to bed primarily because of weakness. The course now became intermittent with short spontaneous remissions during which she was able to move all her joints without pain. The fever was now low grade but the erythrocyte sedimentation rate was persistently elevated.

On May 9, 1949, the patient was admitted to Bellevue Hospital. Severe muscle atrophy and weight loss contributed to an appearance of extraordinary emaciation. She was unable to sit up or stand unaided. With support and with much pain she could take a few limping steps. The distal as well as the proximal interphalangeal joints of the fingers of both hands were tender, warm and showed fusiform swelling. The skin over them was darkly pigmented. The patient was unable to form a fist and both wrists and knees were warm, tender and markedly swollen. Flexion of the knees and extension of the wrists were greatly restricted. The elbows, ankles and feet were involved to a lesser degree. Spasm of the muscle groups above the left hip limited abduction, flexion, extension and rotation to less than 50 per cent of normal. The pelvis was tilted upward on the left side, causing apparent shortening of the left leg of 1½ inches.

There were no subcutaneous nodules or splenomegaly. One large epitrochlear lymph node was palpable and not tender.

Urinalyses and blood counts were within normal limits. The titer of antistreptolysin 0 was less than 100 units. Hemolytic streptococcus agglutination and sensitized sheep red cell agglutination tests were negative. Roentgenograms of all joints revealed generalized osteoporosis but no erosion of the articulating cartilages or destruction of juxta-articular bone.

The patient's course during this hospitalization was afebrile. There were no complaints of joint pains at rest except for transient discomfort in her left hip. No specific treatment was given at this time. The patient was discharged on May 30th and was readmitted on July 24, 1949, at which time cortisone was made available to us. Shortly before this admission she experienced transient episodes of exquisite pain in her left hip.

The patient's past history was non-contributory except for common childhood illnesses, rubella, rubeola, varicella and pertussis, all treated at home. There was no family history of diabetes mellitus. Her mother had tuberculosis which was now considered arrested and her father and an only sibling are alive and well.

During a preliminary sixteen-day period of observation the temperature, blood count, urinalyses, concentration of sugar, electrolytes and proteins in the blood and glucose tolerance tests (oral) were all within normal limits. The gamma globulin level of the serum was slightly above normal. The erythrocyte sedimentation rate was persistently elevated to values between 46 and 65 mm. per hour (Westergren method). Swelling of the hands and wrists was determined by the volume of water displaced which at this time measured 240 cc.

Cortisone was started on August 9, 1949; 100 mg. were administered daily for one week then 75 mg. daily for six days, 50 mg. for two days and 25 mg. on the last day of this course. Subjective and objective improvement which was slight but definite after forty-eight hours became striking by the fourth day. The patient who had been completely bedridden was now able to get out of bed and into a wheelchair unaided. Limitation of motion diminished, swelling and finally tenderness of all involved joints decreased. At the end of one week tenderness in all joints was gone.

Glycosuria appeared on the third day of treatment and rapidly increased to 67 gm. in twenty-four hours by the end of the first week; yet the fasting blood sugar had risen to only 117 mg. per cent. Upon decreasing the dose of cortisone to 75 mg. daily there was no diminution in clinical improvement but glucose excretion increased to 97 gm. per twenty-four hours. (Table II, Fig. 1.) On the sixteenth day of cortisone therapy the glucose tolerance test was found to be markedly abnormal. At this time the patient was placed on a controlled diet consisting of

AND LABORATORY CHANGES ASSOCIATED WITH COURSES OF CORTISONE AND ACTH ADMINISTRATION\* TABLE II CLINICAL

	Hormone Administration	lministr	ation	Clinical Improvement	ovement	Weight Gain	ESR † (mm. /hr.)	Glucose I	Glucose Determinations in Blood and Urine	in Blood	Relapse	ipse
Course	Period	Total (mg.)	Average Daily (mg.)	Extent	Time Required (da.)	Average Daily Weight Gain during Course (oz.)		Maximum Fasting Blood Glucose (mg. %)	Maximum Glucose Excretion (gm./day)	Disap- pearance of Glyco- suria after Drug Stopped (da.)	Interval be- tween Stop- ping Drug and Re- lapse (da.)	Degree of Re- lapse‡
Cortisone 1st	8/9-8/24	1275	80	Very marked	6 '	€0 +	78-5	117	97	٠. ک	00 0	(%)
Cortisone 2nd	10/10-12/8	3090	52	Marked	37	1.6	58-10 65-2	112	71	10	o 10	50
thenate)	1/25-2/8	356	24	Slight	11	0.5	54-31	80	None	•	00	100
of course)	3/13-5/19	5300	78	Very marked	11	1.0	28-8	116	85	23	30	25
48 hours)	6/29-8/9	1350	50	Moderate	∞	1.0	16–29	113	Glycosuria intermittent during course; gen- erally none		Patient s getting cortisone	still s me

\* Note the correlation between (1) the daily dose of cortisone and the extent of clinical improvement attained; (2) the total amount of drug administered and the degree of relapse and persistence of glycosuria following withdrawal of drug.

† Erythrocyte sedimentation rate measured by Westergren method. Values stated are before and during treatment.

‡ On basis of status present immediately before specified course was administered.

250 gm. of carbohydrate, 100 gm. of protein and 80 gm. of fat. Cortisone was withdrawn the following day because it was feared that with continued administration the diabetes might become irreversible. Following this first course of cortisone the erythrocyte sedimentation rate had fallen to 10 mm./hour and the serum

severe torticollis developed along with the return of arthritic symptoms in the peripheral joints.

Cortisone was reinstituted beginning with small doses of 10 mg. daily in an attempt to find the minimal effective dose and avoid the recurrence of glycosuria. Clinical improvement was

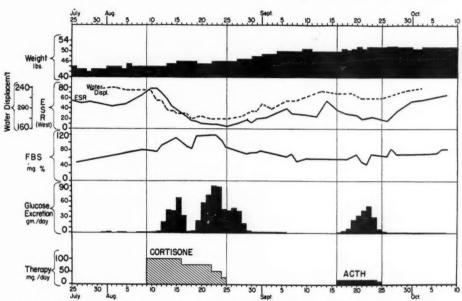


Fig. 1. The effect of cortisone (first course) and ACTH on body weight, erythrocyte sedimentation rate (ESR), water displacement by hands and wrists, fasting blood sugar (FBS) and glucose excretion. The water displacement reflects the degree of swelling.

gamma globulin was normal. Swelling of the hands and wrists was greatly diminished as measured by the water displacement method (180 cc). (Fig. 1.)

Glycosuria disappeared six days after cortisone was stopped. The erythrocyte sedimentation rate began to rise slowly and swelling and tenderness of the proximal interphalangeal and wrist joints were apparent at the end of one week. In three weeks clinical relapse was severe. (Fig. 2.) The fasting blood sugar and glucose tolerance test had returned to normal. (Table III.)

ACTH was then administered, 20 mg. being given daily in four divided doses. Clinical improvement was marked again by the fourth day but glycosuria appeared and by the seventh day rose to 52 gm. in twenty-four hours. The drug was discontinued after nine days. There was prompt and rapid return of arthritic symptoms and in four days the patient was again bedridden. Glycosuria disappeared two days after ACTH was discontinued and the glucose tolerance test, which had again become abnormal, returned to normal by the end of the second week. In the period following this course of therapy

slight and the pelvic tilt and torticollis remained unaltered. Glycosuria, however, did not appear. (Fig. 3.) After nineteen days the dose was increased to 30 mg. daily. Clinical improvement was still incomplete and the urine was free of glucose. After one week the daily amount was raised to 60 mg. daily. Although further improvement was noted, it was not considered maximal and despite the appearance of moderate glycosuria after three days of 60 mg. daily the daily dose was increased to 80 mg. Glucose excretion now became severe and the glucose tolerance test was abnormal. Clinical remission was complete except for the torticollis.

Because of Conn's hypothesis<sup>22</sup> that ACTH exerts its diabetogenic effect by reducing the intracellular availability of free sulfhydryl groups, and his report on the effect of reduced glutathione in partially alleviating the hyperglycemia and glycosuria in a normal subject treated with ACTH, it seemed reasonable to administer BAL (2,3-dimercapto-propanol) which is another source of the sulfhydryl group. The patient, who had marked glycosuria (over 40 gm. in twenty-four hours) and an abnormal



Fig. 2. Plaster casts of right hand and wrist of patient V. M.; note the fusiform swelling of distal as well as proximal interphalangeal joints.

tolerance to oral glucose while on 80 mg. of cortisone daily, was given BAL, 3 mg. per kg. and the levels of glucose in the blood following the test meal were studied. A glucose tolerance test was then carried out while the patient was

hirsutism, acneiform eruption or striae. The patient's appetite had become ravenous and she now appeared well nourished and weighed 60 pounds. This was considered to be a real gain in body weight since there was only minimal

TABLE III GLUCOSE TOLERANCE TESTS (50 GM. GLUCOSE BY MOUTH)

Date	8/5	8/24	9/13	9/15	9/28	10/8	10/28	11/21	11/28	1/6	1/20	2/7	2/21	3/22	4/11	4/18	5/19	6/13	8/8
Cortisone Course.  Day of Course.  Total mg. to Date  Day After Course.  Total mg. for Course.		16 1250	20	22	4	ACTH  14 170	2nd 19 180	2nd 43 1530	2090	29	43	14 319		10 700	30 2300	37 2860	4th 68 5280  5300	25	1300
				В		ucose C mg./100		ration											
Fasting	80 150 117 112	296 356	162 231 174	111	176 207 144	90 188 167 133 72 68	60 117 165 167 132	86 243 192 132 118	214 344	128 208 216	172 236 194	120 252 206	148 208 116	144 244 280	179 335 390	166 290	168 378 410	192 240 205	234 231 16

\* Plus 270 gm. calcium pantothenate (10 gm. daily 1/13/50-2/8/50) † Plus DCA (desoxycorticosterone acetate) 20 mg. daily

DCA omitted for previous week

receiving BAL, but the curve remained markedly abnormal. No significant change was noted when the test was repeated without BAL.

Cortisone was then given in gradually diminishing doses and discontinued after a course of 2,530 mg. Clinical remission was marked except for the torticollis which had only slightly improved. Roentgenographic examination of the cervical spine showed no osseous or cartilaginous changes. At this time rounding and flushing of the face, commonly referred to as "moon face," and "plethora" were apparent. There were no § During most of this course cortisone was administered in single

injections of 50 mg. every 48 hours

|| Test terminated because patient had eaten

sodium and fluid retention and no edema.

Glycosuria disappeared in four days and signs of clinical relapse reappeared. Arthritis of the wrists and hands became severe again by the end of one week although involvement of the other joints was mild. About 75 per cent of the improvement effected was lost (relapse 75 per cent). (Table II.) However, she never again became bedridden or lost weight. Six weeks after the last dose of cortisone the glucose tolerance test was still abnormal and the ESR was again markedly elevated.

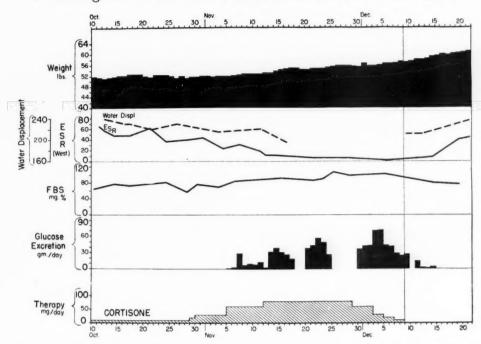


Fig. 3. Second course of cortisone from October 10 to December 10, 1949. When the dotted line indicating displacement is interrupted, no measurements were made. The base line in the column for glucose excretion indicates absence of glucose from the urine. When the base line is not interrupted, quantitative urine collections were not possible because of other tests; glycosuria was present on those days, however.

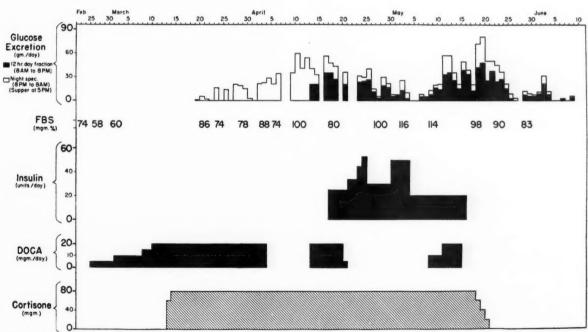


Fig. 4. Fourth course of cortisone from March 13 to May 19, 1950. White columns illustrating the daily amount of glucose excreted from March 19th to April 13th represent twenty-four hour excretions. The columns after April 13th are divided into day and night fractions. The solid black denotes amount of glucose excreted from 8:00 a.m. to 8:00 p.m. and the remainder of the column (white) from 8:00 p.m. to 8:00 a.m. On April 17th, for example, a total of 40.9 gm. was excreted of which 24.4 gm. were in the day specimen and 16.5 gm. in the night specimen. At 8:00 a.m. of the following morning the fasting blood sugar was 80 mg. per cent.

At this point it was suggested that administration of calcium pantothenate might reduce the requirement for cortisone to levels low enough to avoid glycosuria. This was based on the observation reported by Dumm and Ralli<sup>23</sup> that when adrenalectomized rats were fed large doses of pantothenate they not only survived but also appeared well and grew almost normally for a time. The effectiveness of pantothenic acid in maintaining life in the adrenalectomized rat was thought to be related to its action on carbohydrate metabolism.

Since it had been demonstrated that desoxy-corticosterone acetate (DCA) had the capacity to reduce the incidence of diabetes resulting from the administration of alloxan<sup>24</sup> and to increase sensitivity to insulin in human diabetes, <sup>25</sup> it was decided to administer DCA to the patient in the hope that it might counteract the inhibition of carbohydrate utilization resulting from cortisone.

On February 25th when the patient was in



5в

Fig. 5. A, Photograph of V. M. on September 23, 1949; B, same patient on May 23, 1950; the "moon face" is typical of patients getting adrenocortical hormone.

Calcium pantothenate, 10 gm. daily, was administered for twelve days and then cortisone, 25 mg. daily, was administered together with calcium pantothenate for fifteen days. On combined therapy there was no glycosuria but this amount of cortisone previously given alone had not caused glycosuria. Improvement of the arthritis was no greater than it had been when the patient was getting 30 mg. of cortisone without pantothenate and the ESR remained moderately elevated. The slight clinical improvement which had been attained by this measure was rapidly lost when the drugs were withdrawn. Two weeks later relapse was severe and the glucose tolerance test had returned to normal limits.

5A

complete relapse following the third course of cortisone, daily DCA administration was begun. (Fig. 4.) The daily dose was increased from 5 to 20 mg. over a period of sixteen days and then (March 13th) cortisone was added. During the next three weeks when 80 mg. of cortisone together with 20 mg. of DCA were given daily, the excretion of glucose increased, gradually reaching 29 gm. on April 3rd. The pattern was similar to that observed when cortisone alone was administered. Indeed, when DCA was discontinued on April 4th and reinstituted on April 12th for eight days, the degree of glycosuria remained essentially unaffected.

Insulin therapy was introduced on April 19th when the patient was excreting 37 gm. of glucose

daily. With 50 units of crystalline insulin administered in three divided doses, the urine became sugar-free. When insulin was reduced to 20 units, glycosuria returned and mounted as before, uninfluenced by the addition of 20 mg. of DCA daily.

As will be noted from Figure 3, quantitative glucose determinations were made on urines collected during the day (8 A.M. to 8 P.M.) and during the night (8 P.M. to 8 A.M.) in an attempt to determine whether most or all of the excreted glucose was a result of postprandial hyperglycemia or whether a component of it was due to renal glycosuria, a low threshold permitting glucose excretion at normal blood glucose concentrations. The results suggested that a low renal threshold may have been responsible for at least part of the glycosuria. On April 17th, for example, when the patient was getting 80 mg. of cortisone and was on a diet of 250 gm. of carbohydrate, 97 gm. of protein and 81 gm. of fat, she excreted 40.9 gm. of glucose during the twenty-four-hour period, of which 16.5 gm. (40 per cent) were excreted during the night. The fasting blood sugar determined the following morning was 80 mg. per cent. (Fig. 4.)

The fourth course of cortisone which ended on May 19th was the longest; 5,300 mg. were administered over a period of sixty-eight days. Following this course clinical relapse was delayed, and glycosuria as well as abnormal glucose tolerance persisted for a longer period than following previous, shorter courses. (Fig. 5.)

The patient was discharged on June 19th and returned to the arthritis clinic at weekly intervals. When on June 29th relapse became definite, cortisone administration was reinstituted. The patient was given first 75 mg. and later 50 mg. every forty-eight hours. The diet consisted of carbohydrate 250 gm., protein 97 gm. and fat 81 gm. No insulin was administered and the urine was examined daily at home. On this regimen marked clinical improvement was maintained and traces of sugar appeared intermittently in the urine. On August 9, 1950, one year after cortisone was first administered, the urine was free of sugar but the glucose tolerance test was abnormal. (Table III.) The fasting blood sugar concentration was 113 mg. per cent; the ESR was 29 mm. It is noteworthy that the eosinophil test made at this time was normal; four hours following injection of 25 mg. of ACTH the circulating eosinophil count fell



Fig. 6. Photograph of V. M. on June 6, 1950. Besides the "moon face," the excess fat deposit over the cervical vertebrae ("buffalo hump") and in the breast is a result of prolonged adrenocortical hormone administration. The body contour is more mature than in a normal girl of ten.

75 per cent. Clinically the patient was ambulatory, free of joint pains on rest or motion although the wrists and knees were slightly swollen and warm and their range of motion restricted to a minor degree. The pelvic tilt was reduced and apparent shortening of the lower left leg was only 3/4 inch. The torticollis was gone. The patient weighed 79 pounds and generally felt very well. Her physical appearance compared with that before the onset of illness was strikingly different. The facial contours were rounded, the abdomen protuberant and the breast, the spinous processes of the lower cervical vertebrae and the iliac crests well padded with fat. (Fig. 6.) Roentgenographic examination of the hips, knees, ankles, hands, wrists and cervical spine demonstrated no bony destruction or diminution in joint spaces; osteoporosis was absent.

#### SUMMARY

The diabetogenic effect of cortisone\* and ACTH administered intermittently over a period of one year to a girl of ten years with severe rheumatoid arthritis who was nondiabetic and had no family history of diabetes is reported. Improvement in the arthritis was very marked when adrenocortical hormones were given and relapse followed their withdrawal. At the end of one year there was no apparent progression in the joint disease. Glycosuria, relatively mild hyperglycemia and abnormal glucose tolerance were consistently associated with the daily administration of 60 mg. or more of cortisone and 20 mg. of ACTH, but disappeared when these agents were discontinued. The glycosuria responded to insulin but was not affected by DCA or BAL. Calcium pantothenate did not reduce the amount of cortisone required to effect clinical improvement. The disturbance in carbohydrate metabolism did not interfere with the therapeutic efficacy of cortisone or ACTH. The prolonged administration of cortisone was associated with conspicuous deposition of fat in the face, breasts, abdominal wall, over the lower cervical spine and iliac crests.

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## Encephalomyelitis Complicating Antirabies Vaccination Treated with Cortisone

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OSTVACCINAL neurologic complications may occur ten to fourteen days following the first injection of antirabies vaccine. There is much indirect evidence1 that these may be allergic reactions. No virus has been recovered from such cases nor have these syndromes been transmitted from man to animals. The pathology of postvaccinal encephalitic reaction is described2,3 as primarily one of myelin destruction, perivascular lymphocytic infiltration and microglial proliferation with little damage to the nerve cells. This is quite in contrast to the findings in the known neurotropic virus diseases in which there is damage to the nerve cells with inflammatory infiltrations. On the other hand, it is quite similar to the findings in fatal cases of postinfectious encephalitis in which likewise no virus has been recovered. Rivers et al.4 have produced similar pathologic lesions of demyelinization and inflammation in monkeys by intramuscular injections of normal rabbit brain emulsions. More recently Kabat et al.5 and Mayer and his associates have demonstrated that the development of these lesions may be blocked by cortisone and ACTH. Whether these experimental lesions are the same as the disease as seen in man is not known. If postvaccinal neurologic syndromes are hypersensitive reactions, cortisone might be expected to inhibit the pathologic changes and halt the progression of symptoms as it may in other hypersensitive states.

#### CASE REPORT

C. M., a twenty-two year old white male farmer, came to us July 31, 1951, from another county where he had been receiving antirabies vaccine. On July 11th a dog had licked his hands on which there were several small abrasions. Several days later the dog became ill, was thought to be rabid and was shot

through the head destroying its brain. For thirteen days the patient received daily injections of anti-rabies vaccine. The vaccine was a 20 per cent rabbit brain virus, phenol killed. Following the eleventh injection the patient had a headache and some fever. On the twelfth day he felt much worse. His headache was more severe and he had pains in his back, difficulty in starting urination and his temperature was 103°F. However, he received his twelfth injection and was given aspirin for his fever and headache. He was seen by the writer the following day when he complained of severe headache, worse in the occipital region, severe pains in his neck and back, and dysuria. For less than one hour he had noted paresthesias about the mouth characterized by tingling and numbness. His wife stated that he had been sleeping excessively and had been difficult to arouse. He was confused and unable to give an accurate history.

On physical examination the patient appeared to be seriously ill. His temperature was 101°F. His face was pale and he was perspiring freely. There was moderate to marked stiffness of his neck. Kernig's sign was positive. He was tender over the muscles of the back. His pupils were large and equal and reacted to light. He was unable to discriminate between sharp and dull touch over either cheek. Knee and ankle tendon reflexes were quite hyperactive. Biceps reflexes were normal. Abdominal reflexes were absent. There was a positive Babinski on the left. No motor abnormalities of the cranial nerves were demonstrated. Examination of the heart, lungs and abdomen was not remarkable.

Laboratory data were as follows: *Blood counts:* red cells, 5.4 million; hemoglobin, 15.7 gm.; white cells, 8,000. *Differential:* segmented forms 85; juvenile, 2; stabs, 2; lymphocytes, 10; monocytes, 1. The Kahn test and urinalysis were negative. The spinal fluid was clear with

opening pressure of 220 mm. H<sub>2</sub>O; protein, 97 mg. per cent; glucose, 47 mg. per cent; cell count, 62 with 44 per cent polymorphonuclear

cells and 66 per cent lymphocytes.

It was believed that the patient had acute encephalomyelitis and he was admitted to the Rutherford Hospital. Cortisone, 125 mg., was given intramuscularly every eight hours for two days, then 100 mg. every twenty-four hours for four days (total dose 1,125 mg.). The patient was febrile during the first twenty-four hours with temperatures ranging from 100° to 104°F. and he had a severe occipital headache which was not relieved entirely by 1 gr. codeine and 10 gr. aspirin every four hours. He slept almost constantly but was easily aroused and took fluids well by mouth. He had urinary retention on admission and had to be catheterized at intervals during the next six days. He complained of diplopia on looking to either side but no strabismus could be detected.

At the end of twenty-four hours marked improvement had occurred. The patient's temperature was normal; and although when questioned he stated that he still had some headache, he did not request more analgesics. After forty-eight hours he still complained of mild headache and he continued to be drowsy. A second spinal fluid examination showed an opening pressure of 200 mm., the fluid was clear and the dynamics free. Protein was 69 mg. per cent and cell count 5.

Progressive improvement in his sense of well-being continued and no new neurologic findings were detected. On the fourth day he was awake most of the time and talking freely, having little recollection of the past four or five days. By the fifth day there was no stiffness of the neck muscles. He continued to have a positive Babinski on the left, hyperactive knee and ankle reflexes and absent abdominal reflexes. He still complained of paresthesias about the mouth and herpes simplex lesions were developing about the lips. On the sixth day a third spinal fluid examination showed an opening pressure of 190 mm., protein 61.5 mg. per cent and cell count 11. On this day he began to void voluntarily.

He was discharged on the seventh hospital day feeling well, voiding easily and with no headache. Three weeks later there had been no recurrence of symptoms and the patient complained only of feeling weak and nervous. Knee and ankle tendon reflexes, however, remained hyperactive and a left positive Babinski sign still could be elicited. Five weeks after discharge the deep reflexes were normal but the Babinski sign on the left remained positive.

#### COMMENT

Andrew Jones<sup>7</sup> in a recent clinico-pathologic conference at the Washington University School of Medicine noted that they had encountered twelve patients with neurologic disease arising on the basis of antirabies therapy in the past twenty-five years. He remarked that the time of onset was variable depending in part on the type of vaccine employed. At that conference the problem of these complications was reviewed and a fatal case was presented in which 100 mg. of cortisone had been given to the patient before he expired.

#### SUMMARY

A case of encephalomyelitis complicating antirables vaccination is reported in which there appeared to be a dramatic response to cortisone therapy.

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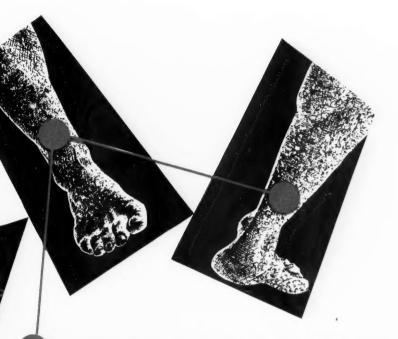
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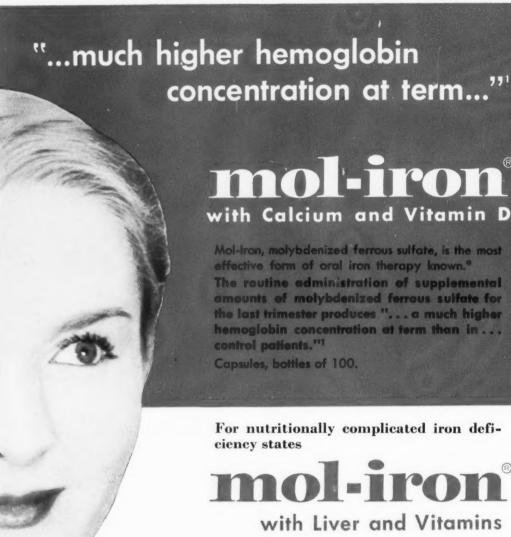


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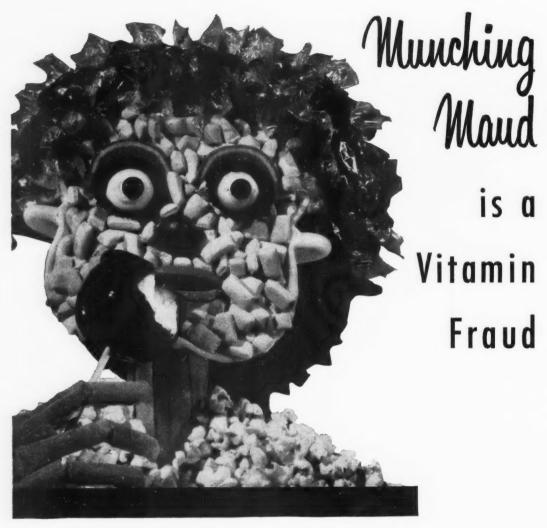
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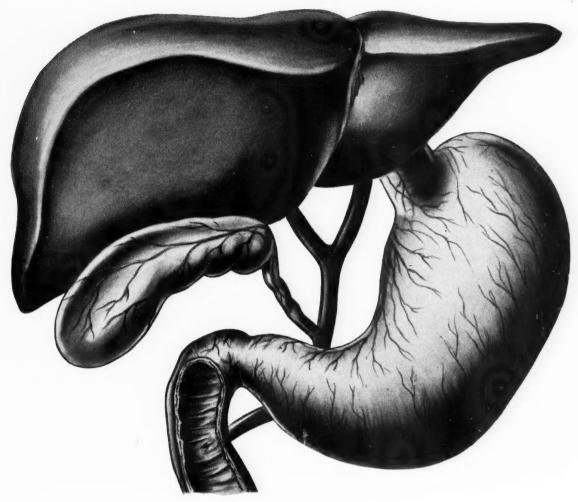
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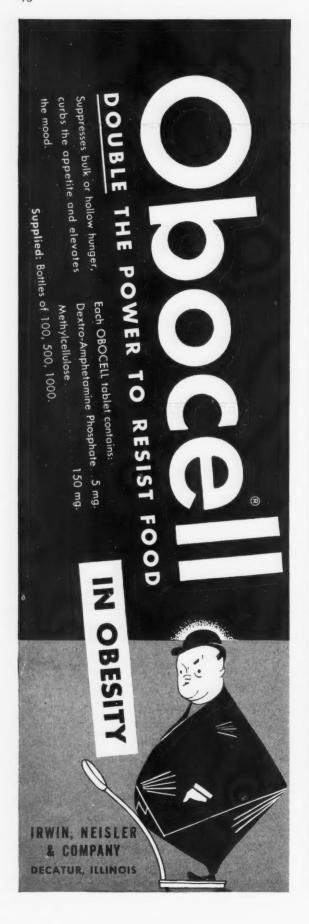
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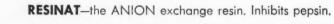
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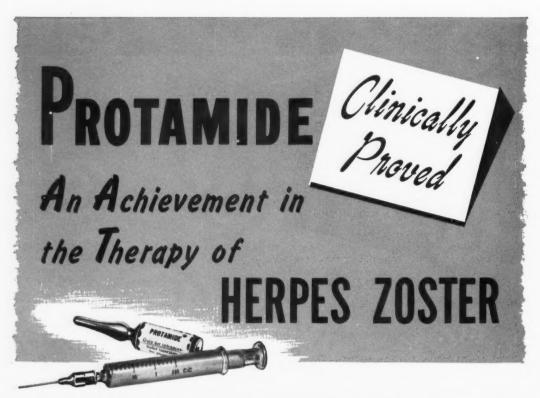
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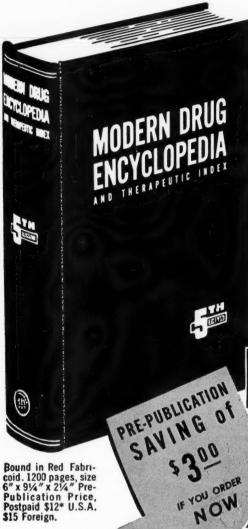
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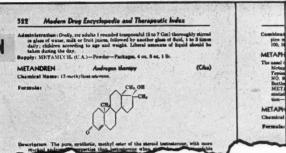


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